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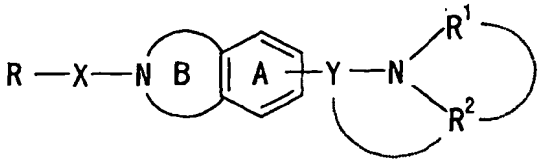
(54) MELANIN-CONCENTRATING HORMONE ANTAGONIST

(57) A melanin-concentrating hormone antagonist comprising a compound of the formula:



(I)

wherein R is hydrogen atom or a cyclic group which may be substituted; X is a bond or a spacer having a main chain of 1 to 10 atoms; Y is a spacer having a main chain of 1 to 6 atoms; ring A is benzene ring which may be further substituted; ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted; R^1 and R^2 are the same or different and are hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic ring which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing heterocyclic ring which may be substituted; or a salt thereof is useful as a preventive or therapeutic agent for obesity, etc.

EP 1 283 199 A1

Description

TECHNICAL FIELD

[0001] The present invention relates to a melanin-concentrating hormone antagonist which is useful as an agent for preventing or treating obesity, etc.

BACKGROUND ART

[0002] Feeding behavior is an essential action for many living beings including humans. Therefore, if irregularities in feeding behavior occur, disorders, often connected to diseases, will occur in normal life-maintaining activities. Accompanying recent changes of our dietary environment, obesity is now becoming a social problem. In addition, not only is obesity a serious risk factor for life-style diseases such as diabetes, hypertension, and arteriosclerosis; it is also widely known that increased body weight places excessive burdens on joints such as knee joints, causing arthritis and pain. The "diet boom," etc. show that there is a potentially great percentage of the population hoping to reduce body weight; on the other hand, many cases of feeding problems such as overeating, occurring due to causes such as hereditary neurosis or neurosis due to stress, have been reported.

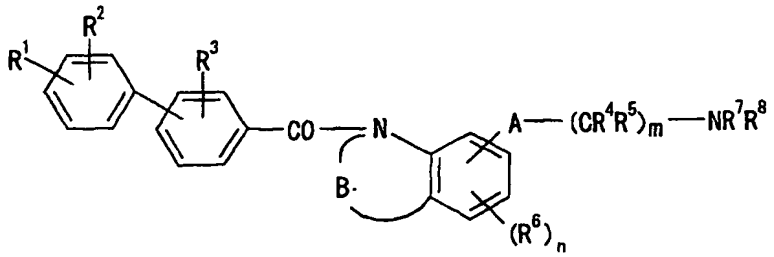
[0003] Therefore, research on and development of agents for preventing or treating obesity, or agents for inhibiting eating, have been vigorously done for a long time. The centrally acting anorectic drug, Mazindol, is now being marketed.

[0004] Many appetite control factors such as leptin, have recently been discovered, and the development of anti-obesity agents or anorectic agents which will regulate the functions of these appetite control factors is progressing. In particular, it is known that melanin-concentrating hormone (hereinafter also abbreviated as "MCH") originates in the hypothalamus and has orexigenic action. In addition, it has been reported that even though the daily behavior of MCH knock-out mice was normal, the amount of feeding by MCH knock-out mice was significantly reduced and their body weights were lighter than those of normal mice [Nature, Vol. 396, p.670, 1998]. This indicates that, if a MCH antagonist was produced, it can be expected to be an excellent anorectic agent or anti-obesity agent; but at present there are no known compound, especially non-peptide type compounds, which possess MCH antagonistic actions.

[0005] On the other hand, the following compounds are known as amine derivatives.

1) JP 10-504315 A describes a compound represented by the formula:

[0006]



wherein R^1 is hydrogen, halogen, C_{1-6} alkyl, C_{3-6} cycloalky, COC_{1-6} alkyl, C_{1-6} alkoxy, hydroxy, hydroxy-C_{1-6} alkyl, hydroxy-C_{1-6} alkoxy, acyl, nitro, trifluoromethyl, cyano, CHO, SR^9, SOR^9, SO_2R^9, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $NR^{10}SO_2R^{11}$, $CONR^{10}R^{11}$, $CO_2NR^{10}R^{11}$, $CONR^{10}(CH_2)_pCO_2R^{11}$, $(CH_2)_pNR^{10}R^{11}$, $(CH_2)_pCONR^{10}R^{11}$, $(CH_2)_pNR^{10}COR^{11}$, $(CH_2)_pCO_2$-C_{1-6} alkyl, $CO_2(CH_2)_pOR^{10}$, $CONHNR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}CO_2R^{11}$, $NR^{10}CONR^{10}R^{11}$, CR^{10}=NOR^{11}, CNR^{10}=NOR^{11} (wherein R^{10} and R^{11} are independently hydrogen, or C_{1-6} alkyl and p is 1 to 4) ;

R^2 and R^3 are independently hydrogen, halogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{1-6} alkoxy, acyl, aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, hydroxy-C_{1-6} alkyl, C_{1-6} alkyl-O-C_{1-6} alkyl, CO_2R^{10}, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ (wherein R^{10} and R^{11} are independently hydrogen, or C_{1-6} alkyl);

R^4 and R^5 are independently hydrogen or C_{1-6} alkyl;

R^6 is hydrogen, halogen, hydroxy, C_{1-6} alkyl or C_{1-6} alkoxy;

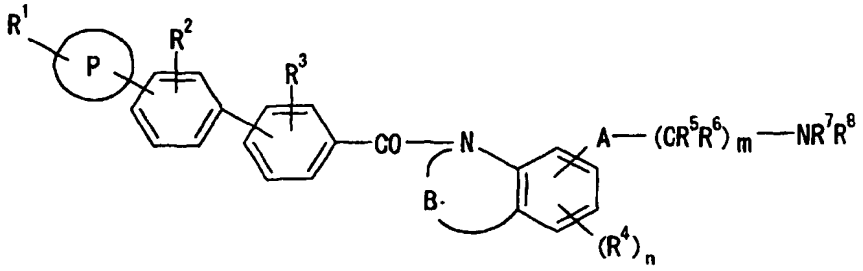
R^7 and R^8 are independently hydrogen, C_{1-6} alkyl, aralkyl or they, together with the nitrogen to which they are attached, may form a 5- to 7-heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen and sulfur which may be substituted;

A is oxygen, $S(O)_q$ (wherein q is 0, 1 or 2), $CR^4=CR^5$ or CR^4R^5 (wherein R^4 and R^5 are independently hydrogen or C_{1-6} alkyl), or A is NR^{12} (wherein R^{12} is hydrogen or C_{1-6} alkyl);
B is $(CR^{13}R^{14})_q$ (wherein q is 2, 3 or 4, R^{13} and R^{14} are independently hydrogen or C_{1-6} alkyl), or B is $(CR^{13}R^{14})_r$-D (wherein r is 0, 1 or 2, D is oxygen, sulfur or $CR^{13}=CR^{14}$);
m is 1 to 4; and n is 1 or 2; or a salt thereof, which has 5-HT_{1D} antagonistic activity.

[0007] As specific examples thereof, there are described 1-(4'-acetamidomethyl-2'-methylbiphenyl-4-carbonyl)-5-chloro-2,3-dihydro-6-(2-dimethylaminoethoxy)-1H-indole, 1-(4'-acetamidomethyl-2'-methylbiphenyl-4-carbonyl)-2,3-dihydro-6-(3-dimethylaminopropyl)-5-ethoxy-1H-indole, etc.

2) JP 9-506885 A (WO95/17398) describes a compound represented by the formula:

[0008]

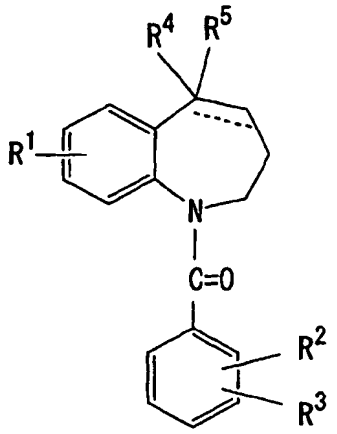


wherein P is a 5- to 7-membered heterocyclic ring containing one to three heteroatoms selected from oxygen, nitrogen and sulfur;
R^1, R^2 and R^3 are independently hydrogen, halogen, C_{1-6} alkyl, C_{3-6} cycloalky, C_{3-6} cylcoalkenyl, C_{1-6} alkoxy, acyl aryl, acyloxy, hydroxy, nitro, trifluoromethyl, cyano, CO_2R^9, $CONR^{10}R^{11}$, $NR^{10}R^{11}$ (wherein R^9, R^{10} and R^{11} are independently hydrogen, or C_{1-6} alkyl);
R^4 is hydrogen, halogen, hydroxy, C_{1-6} alkyl or C_{1-6} alkoxy;
R^5 and R^6 are independently hydrogen or C_{1-6} alkyl;
R^7 and R^8 are independently hydrogen, C_{1-6} alkyl, aralkyl or they, together with the nitrogen to which they are attached, may form a 5- to 7-heterocyclic ring containing one or two heteroatoms selected from oxygen, nitrogen and sulfur which may be substituted;
A is oxygen, $S(O)_n$ (wherein n is 0, 1 or 2), or A is NR^{12} (wherein R^{12} is hydrogen or C_{1-6} alkyl), or A is $CR^5=CR^6$ or CR^5R^6 (wherein R^5 and R^6 are independently hydrogen or C_{1-6} alkyl);
m is 1 to 4;
n is 1 or 2;
B is $(CR^{13}R^{14})_q$ (wherein q is 2, 3 or 4, R^{13} and R^{14} are independently hydrogen or C_{1-6} alkyl), or B is $(CR^{13}R^{14})_r$-D (wherein r is 0, 1 or 2, D is oxygen, sulfur or $CR^{13}=CR^{14}$); or a salt thereof, which has 5-HT_{1D} antagonistic activity.

[0009] As specific examples thereof, there are described [7-(2-dimethylaminoethoxy)-6-methoxy-3,4-dihydro-2H-quinolin-1-yl]-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methanone, [7- (2-dimethylaminopropyl) -6-methoxy-3,4-dihydro-2H-quinolin-1-yl]-[2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methanone, etc.

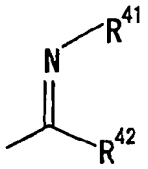
3) JP 6-211800 A describes a compound represented by the formula:

[0010]

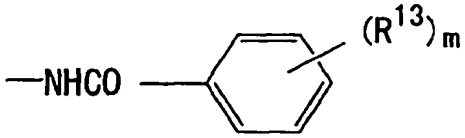


wherein R^1 is hydrogen atom, a halogen atom, hydroxy group, a lower alkanoyloxy group, amino-lower alkoxy group which may have a group selected from a lower alkyl group and a lower alkanoyl group as a substituent, a carboxy-substituted lower alkoxy group, a lower alkoxycarbonyl-substituted lower alkoxy group, or an aminocarbonyl lower alkoxy group which may have a lower alkyl group as a substituent; R^4 is hydrogen atom, a group of $-NR^6R^7$ (wherein R^6 and R^7 are the same or different and are hydrogen atom, a lower alkyl group, a lower alkenyl group or benzoyl group having a halogen atom on the phenyl ring), a lower alkenyloxy group, a hydroxy-substituted lower alkyl group, a group of $-O-CO-ANR^8R^9$ (wherein A is a lower alkylene group, R^8 and R^9 are the same or different and are hydrogen atom or a lower alkylene group, or R^8 and R^9, together with the nitrogen atom to which they are attached, may form a 5-to 6-membered saturated or unsaturated heterocyclic ring through or without through oxygen or nitrogen atom, said heterocyclic ring may have a lower alkyl group on the heterocyclic ring as a substituent), a group of $-O-R^{10}$ (R^{10} is an amino acid residue), a lower alkoxycarbonyl-substituted lower alkylidene group, a lower alkoxycarbonyl-substituted lower alkyl group, a carboxy-substituted lower alkyl group, a group of $-ACONR^{11}R^{12}$ (A is as defined above, R^{11} and R^{12} are the same or different and are hydrogen atom, a lower alkyl group which may have hydroxy group, piperidinyl group which may have a phenyl-lower alkyl group on the piperidine ring, a carbamoyl-substituted lower alkyl group, a pyridyl-substituted lower alkyl group, pyridyl group, a group of $-ANR^{39}R^{40}$ (A is as defined above, R^{39} and R^{40} are the same or different and are hydrogen atom or a lower alkyl group which may have hydroxy group, or R^{39} and R^{40}, together with the nitrogen atom to which they are attached, may form a 5- to 6-membered saturated heterocyclic ring thorough or without thorough nitrogen or oxygen atom, said heterocyclic ring may have a lower alkyl on the heterocyclic ring as a substituent), a pyrazinyl-substituted lower alkyl group which may have a lower alkyl group on the pyrazine ring as a substituent, a pyrrolyl-substituted lower alkyl group which may have a lower alkyl group on the pyrrole ring, a pyrrolidinyl-substituted lower alkyl group which may have a lower alkyl group on the pyrrolidine ring, or phenyl group which may have a halogen atom on the phenyl ring, or R^{11} and R^{12}, together with the nitrogen atom to which they are attached, may form a 5- to 7-membered heterocyclic ring through or without thorough nitrogen or oxygen atom, said heterocyclic ring may be substituted with a lower alkyl group or a pyrrolidinylcarbonyl-lower alkyl group, each of which may have one to two groups selected from the group consisting of a lower alkyl group, a lower alkoxycarbonyl group, amino group which may have a group selected from the group consisting of a lower alkyl group or a lower alkanoyl group as a substituent, a lower alkoxycarbonyl-substituted lower alkyl group, phenyl group which may have a halogen atom on the phenyl ring, a cyano-substituted lower alkyl group, a lower alkenyl group, an oxiranyl-substituted lower alkyl group, a carbamoyl-substituted lower alkyl group and amino group which may have hydroxy group and a lower alkyl group as a substituent), a group $-OACONR^{23}R^{24}$ (A is as defined above, R^{23} and R^{24} are the same or different and are hydrogen atom, a lower alkyl group, a lower alkoxycarbonyl-substituted lower alkyl group, a carboxy-substituted lower alkyl group, piperidinyl group which may have a lower alkyl group on the piperidine ring, or a group of $-B-NR^{23A}R^{24A}$ (wherein B is a lower alkylene group, R^{23A} and R^{24A} are the same or different and are hydrogen atom or a lower alkyl group, or R^{23A} and R^{24A}, together with the nitrogen atom to which they are attached, may form a 5- to 6-membered saturated heterocyclic ring through or without through nitrogen atom or oxygen atom), or R^{23} and R^{24}, together with the nitrogen atom to which they are attached, may form a 5-to 7-membered saturated heterocyclic ring through or

without through nitrogen atom or oxygen atom, said heterocyclic ring may have a lower alkyl group on the heterocyclic ring as a substituent), a pyrrolidinylcarbonyl-lower alkoxy group having a lower alkoxycarbonyl group on the pyrrolidine ring, a lower alkoxy-substituted lower alkanoyloxy group, a group of -BOCOANR^{25}R^{26} (A is as defined above, B is lower alkylene group, R^{25} and R^{26} are the same or different and are hydrogen atom or a lower alkyl group), amino-substituted lower alkylidene group which may have a lower alkyl group as a substituent, a group of -OANR^{27}R^{28} (A is as defined above, R^{27} and R^{28} are the same or different and are hydrogen atom, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a lower alkylsulfonyl group, an aminothiocarbonyl group which may have a lower alkyl group as a substituent, a group of

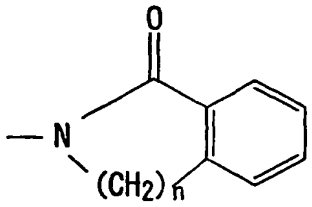


wherein R^{41} is hydrogen atom or cyano group, R^{42} is a lower alkyl group or amino group which may have a lower alkyl group as a substituent), carbamoyl group, a lower alkoxycarbonyl group, cycloalkyl group, a phenyl-lower alkyl group which may have a halogen atom as a substituent on the phenyl group, a cyano-substituted lower alkyl group, a halogen atom-substituted lower alkylsulfonyl group or an amino-substituted lower alkyl group which may have a lower alkyl group, or R^{27} and R^{28}, together with the nitrogen atom to which they are attached, may form a 5- to 10-membered monocyclic or bicyclic, and saturated or unsaturated heterocyclic ring, said heterocyclic ring may have oxo group, a lower alkyl group, a lower alkoxycarbonyl group, a lower alkanoyl group or a lower alkanoylamino group on the heterocyclic ring as a substituent), cyano group, a cyano-substituted lower alkyl group, a lower alkoxy group having phenylsulfonyloxy group whose phenyl ring may have a lower alkyl group as a substituent or hydroxy group, a group -ANR^{29}R^{30} (A is as defined above, R^{29} is hydrogen atom or a lower alkyl group, R^{30} is a lower alkenyl group, cycloalkyl group or a lower alkynyl group, or R^{29} and R^{30}, together the nitrogen atom to which they are attached, may form a 5- or 6-membered saturated heterocyclic ring through or without through nitrogen atom or oxygen atom, said heterocyclic ring may have a lower alkyl group, a lower alkanoyl group, amino group which may have a group selected from the group consisting of a lower alkyl group and a lower alkanoyl group, a lower alkylsulfonyl group, a lower alkoxycarbonyl group, or aminocarbonyl group which may be substituted with a lower alkyl group on the heterocyclic ring as a substituent), a phenylsulfonyloxy-substituted lower alkyl group which may have an lower alkyl group on the phenyl ring, a phthalimide-substituted lower alkyl group, a cyano-substituted lower alkylidene group, a halogen atom-substituted alkyl group, an imidazolyl-substituted lower alkyl group, 1, 2, 4-triazolyl-substituted lower alkoxy group, 1, 2, 3, 4-tetrazolyl-substitued lower alkoxy group, 1, 2, 3, 5-tetrazolyl-substitued lower alkoxy group, 1, 2, 3, 4-tetrazolyl-substituted lower alkyl group, 1, 2, 3, 5-tetrzolyl-substituted lower alkyl group, 1, 2, 4-triazolyl-substituted lower alkyl group, a carboxy-substituted lower alkoxy group, a lower alkoxycarbonyl-substituted lower alkoxy group, a pyridylthio-substituted lower alkoxy group, a pyrimidinylthio-substituted lower alkoxy group which may have a lower alkyl group on the pyrimidine ring, an imidazolylthio-substituted lower alkoxy group, a pyridylsulfinyl-substituted lower alkoxy group, a pyridylsulfonyl-substituted lower alkoxy group, an imidazolylsulfinyl-substituted lower alkoxy group or an imidazolylsulfonyl-substituted lower alkoxy group; R^{5} is hydrogen atom or hydroxy group, or R^{4} and R^{5} together form oxo group; R^{2} is hydrogen atom, a lower alkyl group, hydroxy group, a halogen atom or a lower alkoxy group; R^{3} is a group of

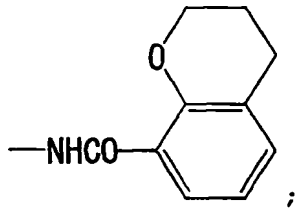


(wherein R^{13} is a halogen atom, hydroxy group, carbamoyl group, a lower alkyl group, a piperazinyl-lower alkoxy group having a lower alkanoyl group at 4-position of the piperazine ring, an imidazolyl-substituted lower alkoxy group, piperidinyl-lower alkoxy group having a lower alkanoylamino group on the piperidine ring, a 1, 2, 4-triazolyl-substituted lower alkoxy group, a ureido-substituted lower alkoxy group which may have a lower alkyl group or an amino-substituted lower alkoxy group which may have a lower alkyl group as a substituent; m is 0 or an integer of 1 to 3, a phenyl-lower

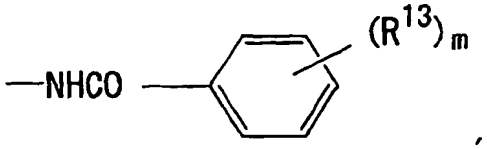
alkanoylamino group which have one to three groups selected from the group consisting of a halogen atom, a lower alkoxy group, a lower alkyl group and nitro group on the phenyl ring as a substituent, a group of



(n is 1 or 2) or a group of



the bond between 4 and 5 positions of the benzazepine ring represent a single bond or a double bond; provided that, when R^1 is hydrogen atom or a halogen atom, and R^4 is hydrogen atom, a group of $-NR^6R^7$ (R^6 and R^7 are the above R^6 and R^7 other than benzoyl group having a halogen atom on the phenyl ring as a substituent), a group of $-O-CONR^8R^9$ (A is as defined above, R^8 and R^9 are the same or different and are hydrogen atom or a lower alkyl), a hydroxy group-substituted lower alkyl group, a carboxy-substituted lower alkoxy group, a lower alkoxycarbonyl-substituted lower alkoxy group or a group $-O-A-NR^{27}R^{28}$ (A is as defined above, R^{27} and R^{28} are the same or different and are hydrogen atom or a lower alkyl group), R^5 is hydrogen atom or hydroxy group or R^4 and R^5 together form oxo group, and further R^3 is a group of



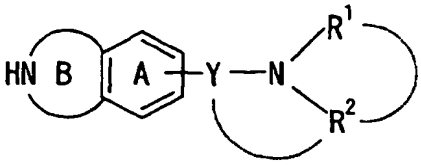
R^{13} must be carbamoyl group, a piperazinyl-lower alkoxy group having a lower alkanoyl group at 4-position of the piperazine ring, a piperidinyl-lower alkoxy group having a lower alkanoylamino group on the piperidine ring, 1, 2, 4-triazolyl-substituted lower alkoxy group or a ureido-substituted lower alkoxy group which may have a lower alkyl group; or a salt thereof, which has vasopressin antagonistic activity or oxytocin antagonistic activity.

[0011] As specific examples, there are described N-[4-[[7-[3-(dimethylamino)propoxy]-2,3,4,5-tetrahydro-1H-1-benzazepin-1-yl]carbonyl]phenyl]-2-methylbenzamide, etc.

[0012] There has been great desire for the development of a melanin-concentrating hormone antagonist which is useful as an agent for preventing or treating obesity, excellent in oral absorbency, and safe.

DISCLOSURE OF INVENTION

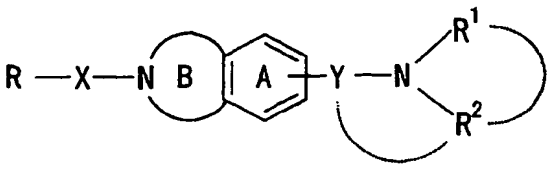
[0013] As a result of intensive studies of compounds with a MCH antagonistic action, the present inventors found that a derivative which is obtained by introducing a group of the formula: R-X- where each symbol is as defined hereafter, into a compound of the formula:



wherein each symbol is as defined hereinafter, had an excellent MCH antagonistic actions, to complete the present invention.

[0014] Namely, the present invention relates to:

1) A melanin-concentrating hormone antagonist which comprises a compound represented by the formula:



(I)

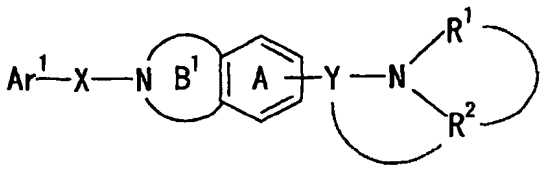
wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
Y is a spacer having a main chain of 1 to 6 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted; and
R^1 and R^2 are the same or different and are hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic ring which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing heterocyclic ring which may be substituted;
or a salt thereof;

2) The antagonist according to the above 1), wherein R is a cyclic group which may be substituted; X is a spacer having a main chain of 1 to 6 atoms; and R^1 and R^2 are the same or different and are hydrogen atom or a hydrocarbon group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, form a nitrogen-containing heterocyclic ring which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, form a nitrogen-containing heterocyclic ring which may be substituted;

3) The antagonist according to the above 1) which is an agent for preventing or treating diseases caused by melanin-concentrating hormone;

4) The antagonist according to the above 1) which is an agent for preventing or treating obesity;

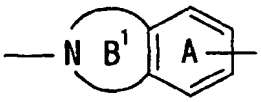
5) A compound represented by the formula:



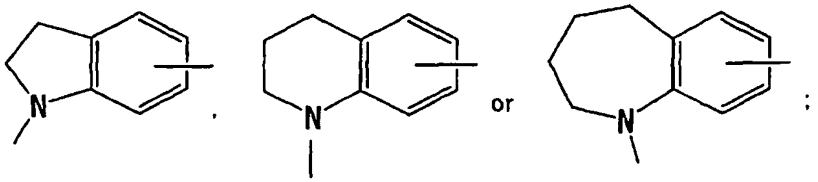
(I')

wherein Ar^1 is a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
Y is a spacer having a main chain of 1 to 6 atoms;
ring A is benzene ring which may be further substituted;
ring B^1 is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted; and

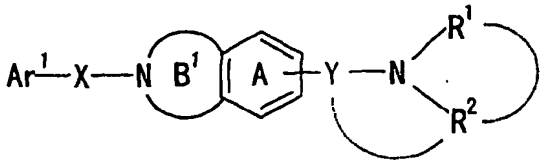
R^1 and R^2 are the same or different and are hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic ring which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing heterocyclic ring (except piperidine) which may be substituted;
provided that, when X is CO, ring B^1 is not azepane or 4,5-dihydroazepine each of which may be further substituted, or Ar^1 is not biphenylyl which may be substituted, and that Y is not -CO-$(C(Ra)H)_{na}$- (Ra is hydrogen atom or a hydrocarbon group which may be substituted, na is an integer of 1 to 10) and does not have a bicyclic nitrogen-containing heterocyclic ring substituted with amino group; or a salt thereof;
6) The compound according to the above 5), wherein X is a spacer having a main chain of 1 to 10 atoms; and R^1 and R^2 are the same or different and are hydrogen atom or a hydrocarbon group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, form a nitrogen-containing heterocyclic ring which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, form a nitrogen-containing heterocyclic ring (except piperidine) which may be substituted;
7) The compound according to the above 5), wherein the cyclic group represented by Ar^1 is an aromatic group;
8) The compound according to the above 7), wherein the aromatic group is a group formed by removing an optional one hydrogen atom from an aromatic ring assembly formed by 2 or 3 members selected from C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon and 5- to 10-membered aromatic heterocyclic ring;
9) The compound according to the above 5), wherein the spacer represented by X and Y is a bivalent group consisting of 1 to 3 members selected from -O-, -S-, -CO-, -SO-, $-SO_2$-, $-NR^8$- (R^8 is hydrogen atom, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkyl-carbonyl or optionally halogenated C_{1-6} alkylsulfonyl), and a divalent C_{1-6} non-cyclic hydrocarbon group which may be substituted;
10) The compound according to the above 5), wherein X is CO;
11) The compound according to the above 5), wherein Y is C_{2-6} alkenylene which may be substituted;
12) The compound according to the above 5), wherein the group represented by the formula:



is



13) The compound according to the above 5), wherein R^1 and R^2, together with the adjacent nitrogen atom, form a nitrogen-containing heterocyclic ring which may be substituted;
14) The compound according to the above 5), wherein R^1 and R^5 are C_{1-6} alkyl;
15) A pharmaceutical composition comprising the compound according to the above 5), or a salt thereof;
16) A prodrug of the compound according to the above 5) ;
17) A process for producing a compound represented by the formula:



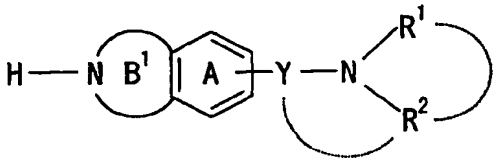
(I')

wherein each symbol is as defined in the above 5), or a salt thereof, which comprises reacting a compound rep-

resented by the formula:

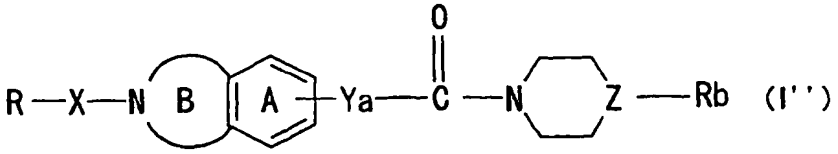
$$Ar^1—X—L \quad (IIb)$$

wherein L is a leaving group and the other symbols are as defined above, or a salt thereof with a compound represented by the formula:



(IIIb)

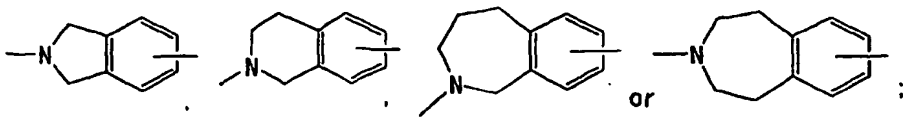
wherein each symbol is as defined above, or a salt thereof;
18) A compound represented by the formula:



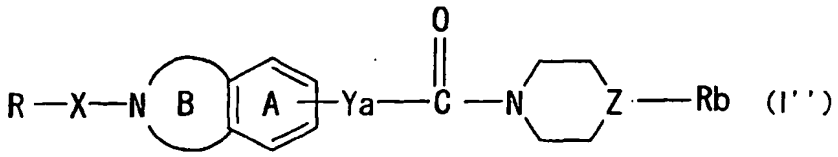
(I'')

wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
Ya is a spacer having a main chain of 1 to 5 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted;
Z is CH or N; and
Rb is hydrogen atom or a hydrocarbon group which may be substituted;
provided that Ya does not have a bicyclic nitrogen-containing heterocyclic ring substituted with amino group; or a salt thereof;
19) The compound according to the above 18), wherein R is hydrogen atom;
20) The compound according to the above 18), wherein Ya is $-(CH_2)_{w1}CO(CH_2)_{w2}-$ (w1 and w2 are an integer of 0 to 5 and w1 + w2 is 0 to 5);
21) The compound according to the above 18), wherein Z is CH;
22) The compound according to the above 18), wherein Rb is C_{6-14} aryl which may be substituted;
23) The compound according to the above 18), wherein the group represented by the formula:

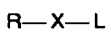
is



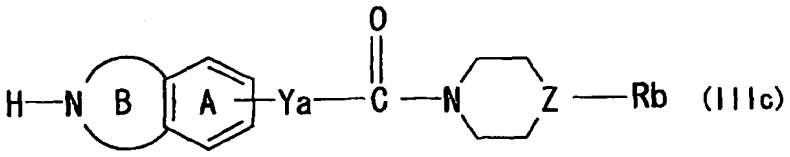
24) A pharmaceutical composition comprising the compound according to the above 18), or a salt thereof;
25) A prodrug of the compound according to the above 18);
26) A process for producing a compound represented by the formula:



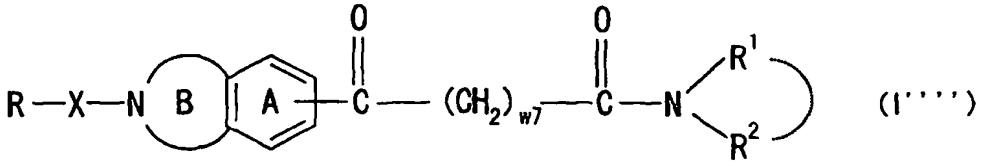
wherein each symbol is as defined in the above 18), or a salt thereof, which comprises reacting a compound represented by the formula:



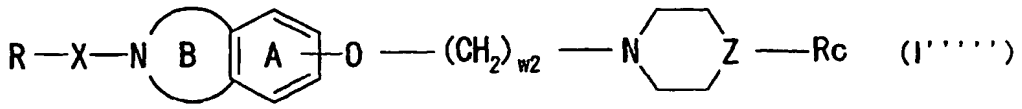
wherein L is a leaving group and the other symbols are as defined above, or a salt thereof, with a compound represented by the formula:



wherein each symbol is as defined above, or a salt thereof;
27) A compound represented by the formula

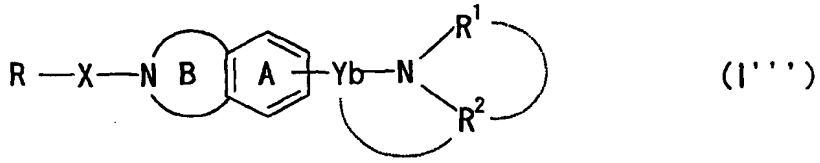


wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted;
w7 is an integer of 0 to 4; and
R^1 and R^2 are the same or different and are hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic ring which may be substituted; or a salt thereof;
28) A pharmaceutical composition comprising the compound according to the above 27) or a salt thereof;
29) A prodrug of the compound according to the above 27);
30) A compound represented by the formula:



(I''''')

wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic group which may be further substituted;
w2 is an integer of 0 to 5;
Z is CH or N;
Rc is a hydrocarbon group which may be substituted;
or a salt thereof;
31) The compound according to the above 30), wherein Z is CH;
32) The compound according to the above 30), wherein Rc is C_{6-14} aryl which may be substituted;
33) A pharmaceutical composition comprising the compound according to the above 30) or a salt thereof;
34) A prodrug of the compound according to the above 30);
35) The antagonist according to the above 1) which is an anorectic agent;
36) A pharmaceutical which comprises the melanin-concentrating hormone antagonist according to the above 1) in combination with at least one species selected from the group consisting of an agent for treating diabetes, an agent for treating hypertension and an agent for treating arteriosclerosis;
37) A method for preventing or treating diseases caused by a melanin-concentrating hormone in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound represented by the formula (I), or a salt thereof;
38) A method for preventing or treating obesity in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound represented by the formula:



(I''')

wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
Yb is a spacer having a main chain of 1 to 6 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted; and
R^1 and R^2 are the same or different and are hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic ring (except piperidine) which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing heterocyclic ring which may be substituted;
provided that Yb is not $-CO-(C(Ra)H)_{na}-$ (Ra is hydrogen atom or a hydrocarbon group which may be substituted, na is an integer of 1 to 10);
or a salt thereof;
39) Use of a compound represented by the formula (I) or a salt thereof, for the manufacture of a pharmaceutical preparation for preventing or treating diseases caused by a melanin-concentrating hormone;
40) Use of a compound represented by the formula (I''') or a salt thereof, for the manufacture of a pharmaceutical preparation for preventing or treating obesity; and the like.

[0015] Examples of the "cyclic group" in the "cyclic group which may be substituted" represented by R and Ar^1 include aromatic groups, non-aromatic cyclic hydrocarbon groups, non-aromatic heterocyclic groups and the like.

[0016] Here, examples of the "aromatic groups" include monocyclic aromatic groups, condensed aromatic groups,

ring assembly aromatic groups and the like.

[0017] Examples of the monocyclic aromatic groups include univalent groups which can be formed by removing an optional one hydrogen atom from a monocyclic aromatic ring. Example of the "monocyclic aromatic ring" include benzene ring and a 5- or 6-membered aromatic heterocyclic ring.

[0018] Examples of the "5- or 6-membered aromatic heterocyclic ring" include a 5- or 6-membered aromatic heterocyclic ring containing one or more (for example, 1 to 3) hetero atoms selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms, and the like. Specifically, thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, furazan, etc., can be mentioned.

[0019] Specific examples of the "monocyclic aromatic groups" include phenyl, 2- or 3-thienyl, 2-, 3-, or 4-pyridyl, 2-or 3-furyl, 2-, 4- or 5-thiazolyl, 2-, 4- or 5-oxazolyl, 1-, 3- or 4-pyrazolyl, 2-pyrazinyl, 2-, 4- or 5-pyrimidinyl, 1-, 2- or 3-pyrrolyl, 1-, 2- or 4-imidazolyl, 3- or 4-pyridazinyl, 3-isothiazolyl, 3-isoxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, etc.

[0020] The "condensed aromatic groups" mean a univalent group that can be formed by removing an optional one hydrogen atom from condensed polycyclic (preferably bicyclic to tetracyclic, more preferably bicyclic or tricyclic) aromatic rings, etc. Examples of the "condensed aromatic groups" include condensed polycyclic aromatic hydrocarbons, condensed polycyclic aromatic heterocyclic rings, etc.

[0021] Examples of the "condensed polycyclic aromatic hydrocarbons" include C_{9-14} condensed polycyclic (bicyclic or tricyclic) aromatic hydrocarbons (e.g. naphthalene, indene, fluorene, anthracene, etc.), etc.

[0022] Examples of the "condensed polycyclic aromatic heterocyclic rings" include 9- to 14-membered, preferably, 9- or 10-membered, condensed polycyclic aromatic heterocyclic rings containing one or more (for example, 1 to 4 atoms) hetero atoms selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms, and the like.

[0023] Specific examples of the "condensed polycyclic aromatic heterocyclic rings" include benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, isoquinoline, quinoline, indole, quinoxaline, phenanthridine, phenothiadine, phenoxazine, phthalazine, naphthyridine, quinazoline, cinnoline, carbazole, β-carboline, acridine, phenazine, phthalimide, thioxanthene, etc.

[0024] Specific examples of the "condensed aromatic groups" include 1-naphthyl; 2-naphthyl; 2-, 3-, 4-, 5- or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 1-, 2-, 4- or 5-isoindolyl; 1-, 5- or 6-phthalazinyl; 2-, 3- or 5-quinoxalinyl; 2-, 3-, 4-, 5- or 6-benzofuranyl; 2-, 4-, 5- or 6-benzothiazolyl; 1-, 2-, 4-, 5- or 6-benzimidazolyl; etc.

[0025] The "ring assembly aromatic group" means a group formed by removing an optional one hydrogen atom from an aromatic ring assembly in which 2 or more (preferably 2 or 3) aromatic rings are directly bonded by single bonds, and in which the number of bonds which directly bond the rings, is less by one than the number of ring systems.

[0026] Examples of the aromatic ring assembly include an aromatic ring assemblies formed by 2 or 3 (preferably 2) species selected from C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbons (e.g. benzene and naphthalene) and 5- to 10-membered (preferably 5 or 6 membered) aromatic heterocyclic rings, etc.

[0027] Preferred example of the aromatic ring assemblies include aromatic ring assembles comprising 2 or 3 aromatic rings selected from benzene, naphthalene, pyridine, pyrimidine, thiophene, furan, thiazole, isothiazole, oxazole, isoxazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, quinoline, isoquinoline, indole, benzothiophene, benzoxazole, benzothiazole and benzofuran.

[0028] Specific examples of the "ring assembly aromatic groups" include 2-, 3- or 4-biphenylyl; 3-(1-naphthyl)-1,2,4-oxadiazol-5-yl; 3-(2-naphthyl)-1, 2, 4-oxadiazol-5-yl; 3-(2-benzofuranyl)-1,2,4-oxadiazol-5-yl; 3-phenyl-1,2,4-oxadiazol-5-yl; 3-(2-benzoxazolyl)-1,2,4-oxadiazol-5-yl; 3-(3-indolyl)-1,2,4-oxadiazol-5-yl; 3-(2-indolyl)-1,2,4-oxadiazol-5-yl; 4-phenylthiazol-2-yl; 4-(2-benzofuranyl)thiazol-2-yl; 4-phenyl-1,3-oxazol-5-yl; 5-phenyl-isothiazol-4-yl; 5-phenyloxazol-2-yl; 4-(2-thienyl)phenyl; 4-(3-thienyl)phenyl; 3-(3-pyridyl)phenyl; 4-(3-pyridyl)phenyl; 6-phenyl-3-pyridyl; 5-phenyl-1,3,4-oxadiazol-2-yl; 4-(2-naphthyl)phenyl; 4-(2-benzofuranyl)phenyl; 4,4'-terphenyl; 5-phenyl-2-pyridyl; 2-phenyl-5-pyrimidinyl; 4-(4-pyridyl)phenyl; 2-phenyl-1,3-oxazol-5-yl; 2,4-diphenyl-1,3-oxazol-5-yl; 3-phenyl-isoxazol-5-yl; 5-phenyl-2-furyl; 4-(2-furyl)phenyl; etc.

[0029] Preferred groups among the above "aromatic groups" are "a group formed by removing an optional one hydrogen atom from an aromatic ring assembly formed by 2 or 3 members selected from a C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon and 5- to 10-membered aromatic heterocyclic ring (preferably, 2-, 3- or 4-biphenylyl; 6-phenyl-3-pyridyl, 5-phenyl-2-pyridyl, etc.)".

[0030] Examples of the "non-aromatic cyclic hydrocarbon groups" include C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, etc.

[0031] Here, specific examples of the C_{3-8} cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl. etc.

[0032] Specific examples of the C_{3-8} cycloalkenyl include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, etc.

[0033] Among the above "non-aromatic cyclic hydrocarbon groups", C_{3-8} cycloalkyl is preferred, and cyclohexyl is particularly preferred.

[0034] Examples of "non-aromatic heterocyclic groups" include monocyclic non-aromatic heterocyclic groups, condensed polycyclic non-aromatic heterocyclic groups, and the like.

[0035] Examples of the "monocyclic non-aromatic heterocyclic groups" include univalent groups formed by removing an optional one hydrogen atom from monocyclic non-aromatic heterocyclic ring. Examples of the "monocyclic non-aromatic heterocyclic ring" include 5- to 8-membered monocyclic non-aromatic heterocyclic rings containing one or more (e.g. 1 to 3) hetero atoms selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Specifically, tetrahydrothiophene, tetrahydrofuran, pyrrolidine, imidazoline, imidazolidine, pyrazoline, pyrazolidine, tetrahydrothiazole, tetrahydroisothiazole, tetrahydrooxazole, tetrahydroisoxazole, piperidine, tetrahydropyridine, dihydropyridine, piperazine, morpholine, thiomorpholine, tetrahydropyrimidine, tetrahydropyridazine, hexamethyleneimine, etc. can be mentioned.

[0036] The "condensed polycyclic non-aromatic heterocyclic group" means a univalent group formed by removing an optional one hydrogen atom from a condensed polycyclic (preferably bicyclic to tetracyclic, more preferably bicyclic or tricyclic) non-aromatic heterocyclic ring. Examples of the "condensed polycyclic non-aromatic heterocyclic ring" include 9- to 14-membered, preferably 9-or 10-membered condensed polycyclic non-aromatic heterocyclic rings which contain one or more (e.g. 1 to 4) hetero atoms selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Specifically, dihydrobenzofuran, dihydrobenzimidazole, dihydrobenzoxazole, dihydrobenzothiazole, dihydrobenzisothiazole, dihydronaphtho[2,3-b]thiophene, tetrahydroisoquinoline, tetrahydroquinoline, indoline, isoindoline, tetrahydroquinoxaline, tetrahydrophenanthridine, hexahydrophenothiadine, hexahydrophenoxazine, tetrahydrophthaladine, tetrahydronaphthyridine, tetrahydroquinazoline, tetrahydrocinnoline, tetrahydrocarbazole, tetrahydro-β-carboline, tetrahydroacridine, tetrahydrophenazine, tetrahydrothioxantene, etc., can be mentioned.

[0037] Among the above "non-aromatic heterocyclic groups", "5- to 8-membered monocyclic non-aromatic heterocyclic groups (preferably piperidino; piperazinyl; pyrrolidinyl; etc.)" are preferred.

[0038] Examples of the "substituent" in the "cyclic group which may be substituted" represented by R and Ar^1 is preferably an aromatic group, more preferably a monocyclic aromatic group (preferably phenyl, pyrrolyl, etc.) or a ring assembly aromatic group (preferably biphenylyl, etc.).

[0039] Examples of the "substituent" in the "cyclic group which may be substituted" represented by R and Ar^1 include oxo, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, C_{6-14} aryloxy-C_{1-6} alkyl (e.g. phenoxymethyl, etc.), C_{1-6} alkyl-C_{6-14} aryl-C_{2-6} alkenyl (e.g. methylphenylethenyl, etc.), optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, C_{7-19} aralkyl which may be substituted, hydroxy, C_{6-14} aryloxy which may be substituted, C_{7-19} aralkyloxy which may be substituted, C_{6-14} aryl-carbamoyl which may be substituted, amino, amino-C_{1-6} alkyl (e.g. aminomethyl, aminoethyl, aminopropyl, aminobutyl, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamine (e.g. dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), mono-C_{1-6} alkylamino-C_{1-6} alkyl (e.g. methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminoethyl, butylaminoethyl, etc.), di-C_{1-6} alkylamino-C_{1-6} alkyl (e.g. dimethylaminomethyl, diethylaminomethyl, dipropylaminomethyl, diisopropylaminoethyl, dibutylaminoethyl, etc.), 5- to 7-membered saturated cyclic amino which may be substituted, 5- to 7-membered non-aromatic heterocyclic groups which may be substituted, acyl, acylamino, acyloxy, etc.

[0040] The "cyclic group" represented by R and Ar^1 may have 1 to 5, preferably 1 to 3, of the above-mentioned substituents at a substitutable position on the cyclic group. When the number of substituents is 2 or more, each substituents can be the same or different.

[0041] Also, when the "cyclic group" represented by R and Ar^1 is a non-aromatic cyclic hydrocarbon group or a non-aromatic heterocyclic group, the "cyclic group" may have as its substituent(s), C_{6-14} aryl which may be substituted, 5-to 10-membered aromatic heterocyclic groups which may be substituted, etc.

[0042] Here, the groups exemplified as the "substituent" in the "5- to 7-membered saturated cyclic amino which may be substituted" mentioned hereinafter, can be mentioned as "C_{6-14} aryl which may be substituted" and "5- to 10-membered aromatic heterocyclic groups which may be substituted". The number of substituents is, for example, 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0043] Specific examples of the above "optionally halogenated C_{1-6} alkyl" include C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Specific examples include methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.

[0044] The C_{1-6} alkyl in the above "optionally halogenated C_{1-6} alkyl" can be mentioned as the C_{1-6} alkyl in the above "hydroxy-C_{1-6} alkyl".

[0045] Examples of the above "optionally halogenated C_{3-6} cycloalkyl" include C_{3-6} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine,

bromine, iodine, etc.). Specific examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4,4-dichlorocyclohexyl, 2,2,3,3-tetrafluorocyclopentyl, 4-chlorocyclohexyl, etc.

[0046] Examples of the above "optionally halogenated C_{1-6} alkoxy" include C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentyloxy, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Specific examples include methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc.

[0047] Examples of the above "optionally halogenated C_{1-6} alkylthio" include C_{1-6} alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.). Specific examples include methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentylthio, hexylthio, etc.

[0048] Examples of the "C_{7-19} aralkyl" in the above "C_{7-19} aralkyl which may be substituted" include benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc. Benzyl is particularly preferred.

[0049] Examples of the "substituent" in the above "C_{7-19} aralkyl which may be substituted" include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), amino-C_{1-6} alkyl (e.g. aminomethyl, aminoethyl, aminopropyl, aminobutyl, etc.), mono-C_{1-6} alkylamino-C_{1-6} alkyl (e.g. methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminoethyl, butylaminoethyl, etc.), di-C_{1-6} alkylamino-C_{1-6} alkyl (e.g. dimethylaminomethyl, diethylaminomethyl, dipropylaminomethyl, diisopropylaminoethyl, dibutylaminoethyl, etc.), formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), mono-C_{1-6} alkyl-carbamoyl (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), optionally halogenated C_{1-6} alkylsulfonyl, formylamino, optionally halogenated C_{1-6} alkyl-carboxamide, C_{1-6} alkoxy-carboxamide (e.g. methoxycarboxamide, ethoxycarboxamide, prpoxycarboxamide, butoxycarboxamide, etc.), C_{1-6} alkylsulfonylamino (e.g. methylsulfonylamino, ethylsulfonylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propanoyloxy, etc.), C_{1-6} alkoxy-carbonyloxy (e.g. methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g. methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g. dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), hydroxy-C_{1-6} alkyl (e.g., hydroxyethyl, etc.), etc. The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0050] As the "optionally halogenated C_{1-6} alkyl", "optionally halogenated C_{3-6} cycloalkyl", "optionally halogenated C_{1-6} alkoxy" and "optionally halogenated C_{1-6} alkylthio", those exemplified as the "substituents" in the above "cyclic group which may be substituted" can be used, respectively.

[0051] Examples of the above "optionally halogenated C_{1-6} alkylcarbonyl" include C_{1-6} alkyl-carbonyl (e.g. acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), etc. Specific examples include acetyl, monochloroacetyl, trifluoroacetyl, trichloroacetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, etc.

[0052] Examples of the above "optionally halogenated C_{1-6} alkylsulfonyl" include C_{1-6} alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, sec-butylsulfonyl, tert-butylsulfonyl, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g., fluorine, chlorine, bromine, iodine, etc.), etc. Specific examples include methylsulfonyl, difluoromethylsulfonyl, trifluoromethylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, 4,4,4-trifluorobutylsulfonyl, pentylsulfonyl, hexylsulfonyl, etc.

[0053] Examples of the above "optionally halogenated C_{1-6} alkyl-carboxamide" include C_{1-6} alkyl-carboxamide (e.g. acetamide, propanamide, butanamide, etc.) which may have 1 to 5, preferably 1 to 3, halogen atoms (e.g. fluorine, chlorine, bromine, iodine, etc.), etc. Specific examples include acetamide, trifluoroacetamide, propanamide, butanamide, etc.

[0054] Examples of the "C_{6-14} aryloxy" in the above "C_{6-14} aryloxy which may be substituted" include phenyloxy, 1-naphthyloxy, 2-naphthyloxy, etc.

[0055] Examples of the "C_{7-19} aralkyloxy" in the above "C_{7-19} aralkyloxy which may be substituted" include benzyloxy, phenethyloxy, diphenylmethyloxy, triphenylmethyloxy, 1-naphthylmethyloxy, 2-naphthylmethyloxy, 2,2-diphenylethyloxy, 3-phenylpropyloxy, 4-phenylbutyloxy, 5-phenylpentyloxy, etc.

[0056] Examples of the "C_{6-14} aryl-carbamoyl" in the above "C_{6-14} aryl-carbamoyl which may be substituted" include phenylcarbamoyl, 1-naphthylcarbamoyl, 2-naphthylcarbamoyl, etc.

[0057] As the "substituents" in the "C_{6-14} aryloxy which may be substituted", "C_{7-19} aralkyloxy which may be substituted" and "C_{6-14} aryl-carbamoyl which may be substituted", those exemplified for the "substituents" in the above "C_{7-19} aralkyl which may be substituted" can be used. The number of substituents is, for example, 1 to 5, preferably 1 to 3.

When the number of substituents is 2 or more, each substituents can be the same or different.

[0058] Examples of the "5- to 7-membered saturated cyclic amino" in the above "5 to 7 membered saturated cyclic amino which may be substituted" include morpholino, thiomorpholino, piperazin-1-yl, piperidino, pirrolidin-1-yl, etc. The "5- to 7-membered saturated cyclic amino" can be condensed with a benzene ring.

[0059] Examples of the "substituent" in the "5- to 7-membered saturated cyclic amino which may be substituted" include oxo, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkylsulfonyl, C_{6-14} aryl which may be substituted, C_{7-19} aralkyl which may be substituted, C_{6-14} aryl-carbonyl which may be substituted, 5- to 10-membered aromatic heterocyclic group which may be substituted, hydroxy, 5- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., piperidinyl, piperazinyl, pyrrolidinyl, etc.), carbamoyl, hydroxy-C_{1-6} alkyl, C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl (e.g. ethoxycarbonylmethyl, etc.), C_{8-19} arylalkenyl (e.g., styryl, 3-phenyl-2-prop-2-enyl, etc.), C_{1-6} alkyl-carboxamide (e.g., methylcarboxamide, etc.), (N-C_{1-6} alkyl)-C_{1-6} alkyl-carboxamide (e.g., (N-ethyl)methylcarboxamide, etc.), amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), 5- to 8-membered monocyclic non-aromatic heterocyclic group-C_{1-6} alkyl (e.g., pyrrolidinylmethyl, etc.), C_{6-14} aryl-amino-C_{1-6} alkyl (e.g., 2,6-dimethylphenylaminomethyl, etc.) which may be substituted with one to three C_{1-6} alkyl, etc. The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0060] Here, as the "optionally halogenated C_{1-6} alkyl" and "C_{7-19} aralkyl which may be substituted", those exemplified as the "substituents" in the above "cyclic group which may be substituted" can be used, respectively.

[0061] Examples of the "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{1-6} alkylsulfonyl" include those exemplified as the "substituents" in the above "C_{7-19} aralkyl which may be substituted".

[0062] Examples of the "C_{6-14} aryl" in the "C_{6-14} aryl which may be substituted" include phenyl, 1-naphthyl, 2-naphthyl, 2-indenyl, 2-anthryl, etc. Phenyl is especially preferable.

[0063] As the "substituents" in the "C_{6-14} aryl which may be substituted", those exemplified as the "substituents" in the above "C_{7-19} aralkyl which may be substituted" can be used. The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0064] Examples of the "C_{6-14} aryl-carbonyl" in the "C_{6-14} aryl-carbonyl which may be substituted" include benzoyl, 1-naphthoyl, 2-naphthoyl, etc.

[0065] As the "substituents" in the "C_{6-14} aryl-carbonyl which may be substituted", those exemplified as "substituents" in the above "C_{7-19} aralkyl which may be substituted" can be used. The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0066] Examples of the "5- to 10-membered aromatic heterocyclic groups" in the "5- to 10-membered aromatic heterocyclic groups which may be substituted" include 5- to 10-membered (monocyclic or bicyclic) aromatic heterocyclic groups containing 1 or 2 kinds of, preferably 1 to 4 hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Specific examples include 2- or 3-thienyl; 2-, 3- or 4-pyridyl; 2- or 3-furyl; 2-, 4- or 5-thiazolyl; 2-, 4- or 5-oxazolyl; 1-, 3- or 4-pyrazolyl; 2-pyrazinyl; 2-, 4- or 5-pyrimidinyl; 1-, 2- or 3-pyrrolyl; 1-, 2- or 4-imidazolyl; 3- or 4-pyridazinyl; 3-isothiazolyl; 3-isoxazolyl; 1,2,4-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl; 2-, 3-, 4-, 5- or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 1-, 2-, 4- or 5-isoindolyl; 1-, 5- or 6-phthalazinyl; 2-, 3- or 5-quinoxalinyl; 2-, 3-, 4-, 5- or 6-benzofuranyl; 2-, 4-, 5- or 6-benzothiazolyl; 1-, 2-, 4-, 5- or 6-benzimidazolyl, etc.

[0067] Examples of the "substituents" in the "5- to 10-membered aromatic heterocyclic groups which may be substituted" include halogen atom (e.g. fluorine, chlorine, bromine and iodine, etc.), C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkyl, C_{6-14} aryloxy-C_{1-6} alkyl (e.g. phenoxymethyl, etc.), C_{1-6} alkyl-C_{6-14} aryl-C_{2-6} alkenyl (e.g. methylphenylethenyl, etc.), optionally halogenated C_{3-6} cycloalkyl, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, C_{7-19} aralkyl which may be substituted, hydroxy, C_{6-14} aryloxy which may be substituted, C_{7-19} aralkyloxy which may be substituted, amino, amino-C_{1-6} alkyl (e.g. aminomethyl, aminoethyl, aminopropyl, aminobutyl, etc.), mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g. dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), mono-C_{1-6} alkylamino-C_{1-6} alkyl (e.g. methylaminomethyl, ethylaminomethyl, propylaminomethyl, isopropylaminoethyl, butylaminoethyl, etc.), di-C_{1-6} alkylamino-C_{1-6} alkyl (e.g. dimethylaminomethyl, diethylaminomethyl, dipropylaminomethyl, diisopropylaminoethyl, dibutylaminoethyl, etc.), 5- to 7-membered saturated cyclic amino, acyl, acylamino, acyloxy, etc. The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0068] Here, as the "optionally halogenated C_{1-6} alkyl", "optionally halogenated C_{3-6} cycloalkyl", "optionally halogenated C_{1-6} alkoxy", "optionally halogenated C_{1-6} alkylthio", "C_{7-19} aralkyl which may be substituted", "C_{6-14} aryloxy which may be substituted", "C_{7-19} aralkyloxy which may be substituted", those exemplified as the "substituents" in the above "cyclic group which may be substituted" can be used, respectively.

[0069] As the "5- to 7-membered saturated cyclic amino", those exemplified as "5-to 7-membered saturated cyclic amino" regarding "5- to 7-membered saturated cyclic amino which may be substituted" which is the "substituent" in

the above "cyclic amino which may be substituted" can be used.

[0070] Examples of the above "acyl" include acyl of the formulas: -CO-R^3, -CO-OR^3, -CO-NR^3R^4, -CS-NR^3R^4, -SO_2-R^{3a}, -SO-R^{3a}, -PO(-OR^3)-OR^4 or -PO_2-R^{3a} wherein R^3 is (i) hydrogen atom, (ii) a hydrocarbon group which may be substituted, or (iii) a heterocyclic group which may be substituted; R^{3a} is (i) a hydrocarbon group which may be substituted, or (ii) a heterocyclic group which may be substituted; R^4 is hydrogen atom or C_{1-6} alkyl; R^3 and R^4, together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic ring which may be substituted, and the like.

[0071] Examples of the "hydrocarbon group" in "hydrocarbon group which may be substituted" represented by R^3 or R^{3a} include straight-chain or cyclic hydrocarbon groups (e.g. alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, arylalkenyl, dihydroindene, etc.), etc. Among these, C_{1-19} straight-chain or cyclic hydrocarbon groups as shown below are preferred.

a) C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.);
b) C_{2-6} alkenyl (e.g., vinyl, allyl, isopropenyl, 2-butenyl, etc.);
c) C_{2-6} alkynyl (e.g. ethynyl, propargyl, 2-butynyl, etc.);
d) C_{3-6} cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.); the C_{3-6} cycloalkyl may be condensed with one benzene ring;
e) C_{6-14} aryl (e.g. phenyl, 1-naphthyl, 2-naphthyl, 2-indenyl, 2-anthryl, etc.), preferably phenyl;
f) C_{7-19} aralkyl (e.g. benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2,2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc.), preferably benzyl, phenethyl, 3-phenylpropyl;
g) C_{8-19} arylalkenyl (e.g., styryl, 3-phenyl-2-prop-2-enyl, etc.);
h) dihydroindene.

[0072] The "hydrocarbon groups" are preferably C_{1-6} alkyl, C_{6-14} aryl, C_{7-19} aralkyl, etc.

[0073] Examples of the "substituent" in the "hydrocarbon groups which may be substituted" include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy, etc.), nitro, cyano, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, hydroxy, amino, mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-(C_{1-6} alkyl optionally substituted with hydroxy)amino (e.g. dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, ethylmethylamino, di(hydroxyethyl)amino, etc.), C_{6-14} arylamino which may be substituted with one to three C_{1-6} alkyl (e.g., phenylamino, 2,6-dimethylphenylamino, etc.), N-C_{1-6} alkyl-N-(C_{6-14} aryl optionally substituted with C_{1-6} alkyl)amino (e.g., N-methyl-N-phenylamino, N-ethyl-N-(methylphenyl)amino, etc.), 5- or 6-membered monocyclic aromatic heterocyclic ring amino optionally substituted with nitro (e.g., nitropyridylamino, etc.), 5- to 8-membered monocyclic non-aromatic heterocyclic group optionally substituted with oxo or C_{1-6} alkyl (e.g., tetrahydrofuryl, pyrrolidinyl, oxopyrrolidinyl, piperidinyl, methylpiperidinyl, morpholinyl, methylpiperazinyl, etc.), formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), 5- to 10-membered aromatic heterocyclic groups which may be substituted, C_{6-14} aryl-carbonyl which may be substituted, C_{6-14} aryloxy-carbonyl which may be substituted, C_{7-19} aralkyloxy-carbonyl which may be substituted, 5- to 6-membered heterocyclic ring-carbonyl which may be substituted, mono-C_{1-6} alkyl-carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C_{6-14} aryl-carbamoyl which may be substituted, 5- to 6-membered heterocyclic ring-carbamoyl which may be substituted, optionally halogenated C_{1-6} alkylsulfonyl, C_{6-14} arylsulfonyl which may be substituted, formylamino, optionally halogenated C_{1-6} alkyl-carboxamide, C_{1-6} alkoxy-carboxamide (e.g., methoxycarboxamide, ethoxycarboxamide, propoxycarboxamide, butoxycarboxamide, etc.), C_{1-6} alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propanoyloxy, etc.), C_{6-14} aryl-carbonyloxy which may be substituted, C_{1-6} alkoxy-carbonyloxy (e.g. methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g. methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g. dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C_{6-14} aryl-carbamoyloxy which may be substituted, nicotinoyloxy, etc. The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0074] Here, as the "optionally halogenated C_{1-6} alkoxy", "optionally halogenated C_{1-6} alkylthio" and "C_{6-14} arylcarbamoyl which may be substituted", those exemplified as the "substituent" in the above "cyclic group which may be substituted" can be used, respectively.

[0075] As the "optionally halogenated C_{1-6} alkyl-carbonyl", "optionally halogenated C_{1-6} alkylsulfonyl" and "optionally halogenated C_{1-6} alkyl-carboxamide", those exemplified as the "substituent" in the above "C_{7-19} aralkyl which may be substituted" can be used, respectively.

[0076] As the above "5- to 10-membered aromatic heterocyclic groups which may be substituted" and "C_{6-14} arylcarbonyl which may be substituted", those exemplified as the "substituent" in the above "5- to 7-membered saturated

cyclic amino which may be substituted" can be used, respectively.

[0077] Examples of the "C_{6-14} aryloxy-carbonyl" in the "C_{6-14} aryloxy-carbonyl which may be substituted" include phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl, etc.

[0078] Examples of the "C_{7-19} aralkyloxy-carbonyl" in "C_{7-19} aralkyloxy-carbonyl which may be substituted" include benzyloxycarbonyl, phenethyloxycarbonyl, diphenylmethyloxycarbonyl, triphenylmethyloxycarbonyl, 1-naphthylmethyloxycarbonyl, 2-naphthylmethyloxycarbonyl, 2,2-diphenylethyloxycarbonyl, 3-phenylpropyloxycarbonyl, 4-phenylbutyloxycarbonyl, 5-phenylpentyloxycarbonyl, etc.

[0079] Examples of the "5- to 6-membered heterocyclic ring-carbonyl" in the above "5- to 6-membered heterocyclic ring-carbonyl which may be substituted" include nicotinoyl, isonicotinoyl, 2-thenoyl, 3-thenoyl, 2-furoyl, 3-furoyl, morpholinocarbonyl, pepiridinocarbonyl, pyrrolidin-1-ylcarbonyl, etc.

[0080] Examples of the "5- to 6-membered heterocyclic ring-carbamoyl" in the above "5- to 6-membered heterocyclic ring-carbamoyl which may be substituted" include morpholinocarbamoyl, pepiridinocarbamoyl, 2-pyridylcarbamoyl, 3-pyridylcarbamoyl, 4-pyridylcarbamoyl, 2-thienylcarbamoyl, 3-thienylcarbamoyl, etc.

[0081] Examples of the "C_{6-14} arylsulfonyl" in the above "C_{6-14} arylsulfonyl which may be substituted" include phenylsulfonyl, 1-naphthylsulfonyl, 2-naphthylsulfonyl, etc.

[0082] Examples of the "C_{6-14} aryl-carbonyloxy" in the above "C_{6-14} aryl-carbonyloxy which may be substituted" include benzoyloxy, 1-naphthoyloxy, 2-naphthoyloxy, etc.

[0083] Examples of the "C_{6-14} aryl-carbamoyloxy" in the above "C_{6-14} aryl-carbamoyloxy which may be substituted" include phenylcarbamoyloxy, naphthylcarbamoyloxy, etc.

[0084] As the "substituents" in the above "C_{6-14} aryloxy-carbonyl which may be substituted", "C_{7-19} aralkyloxy-carbonyl which may be substituted", "5- to 6-membered heterocyclic ring-carbonyl which may be substituted", "5-to 6-membered heterocyclic ring-carbamoyl which may be substituted", "C_{6-14} arylsulfonyl which may be substituted", "C_{6-14} aryl-carbonyloxy which may be substituted" and "C_{6-14} aryl-carbamoyloxy which may be substituted", those exemplified as the "substituents" in the above "C_{7-19} aralkyl which may be substituted" can be mentioned. The number of the substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0085] Examples of the "heterocyclic groups" in the "heterocyclic groups which may be substituted" represented by R^3 or R^{3a} include a 5- to 14-membered (monocyclic, bicyclic or tricyclic) heterocyclic ring containing 1 or 2 kinds of, 1 to 4 hetero atoms selected from nitrogen, sulfur and oxygen atom in addition to carbon atoms. Preferably, univalent groups formed by removing an optional one hydrogen atom from (i) an aromatic heterocyclic ring, (ii) a 5- to 10-membered non-aromatic heterocyclic ring, or (iii) a 7- to 10-membered heterocyclic-bridge ring, etc., can be mentioned.

[0086] Here, examples of the "aromatic heterocyclic ring" include a 5- to 14-membered, preferably 5- to 10-membered, aromatic heterocyclic ring containing one or more hetero atoms (e.g. 1 to 4) selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Specific examples include aromatic heterocyclic rings such as thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, furazan, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, phenoxathiin, indole, isoindole, 1H-indazole, purine, 4H-quinolidine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, β-carboline, phenanthridine, acridine, phenazinephenothiadine, phenoxazine, phthalimide, etc.; or a ring formed by condensing these rings (preferably monocyclic rings) with one to multiple (preferably 1 or 2) aromatic rings (e.g. benzene ring, etc.), etc.

[0087] Examples of "5- to 10-membered non-aromatic heterocyclic rings" include 2- or 3-pyrroline, pyrrolidine, 2- or 3-imidazoline, 2-oxazoline, oxazolidine, 2- or 3-pyrazoline, pyrazolidine, 2-thiazoline, piperidine, piperazine, hexamethylenimine, morpholine, thiomorpholine, etc.

[0088] Examples of "7- to 10-membered heterocyclic-bridge rings" include quinuclidine, 7-azabicyclo[2.2.1]heptane, etc.

[0089] The "heterocyclic groups" are preferably 5- to 10-membered (monocyclic or bicyclic) heterocyclic groups containing 1 or 2 kinds of, preferably 1 to 4, hetero atoms selected from nitrogen, sulfur and oxygen atoms in addition to carbon atoms. Specific examples include aromatic heterocyclic groups such as 2- or 3-thienyl; 2-, 3- or 4-pyridyl; 2- or 3-furyl; 2-, 4- or 5-thiazolyl; 2-, 4- or 5-oxazolyl; 1-, 3- or 4-pyrazolyl; 2-pyrazinyl; 2-, 4- or 5-pyrimidinyl; 1-, 2- or 3-pyrrolyl; 1-, 2- or 4-imidazolyl; 3- or 4-pyridazinyl; 3-isothiazolyl; 3-isoxazolyl; 1,2,4-oxadiazol-5-yl; 1,2,4-oxadiazol-3-yl; 2-, 3-, 4-, 5- or 8-quinolyl; 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 1-, 2-, 4- or 5-isoindolyl; 1-, 5- or 6-phthalazinyl; 2-, 3- or 5-quinoxalinyl; 2-, 3-, 4-, 5- or 6-benzofuranyl; 2-, 3-, 4-, 5- or 6-benzothienyl; 2-, 4-, 5- or 6-benzothiazolyl; 1-, 2-, 4-, 5- or 6-benzimidazolyl; etc.; and non-aromatic heterocyclic groups such as 1-, 2- or 3-pyrrolidinyl; 1-, 2-, 4- or 5-imidazolidinyl; 2- or 4-imidazolinyl; 2-, 3- or 4-pyrazolidinyl; piperidino; 2-, 3- or 4-piperidyl; 1- or 2-piperazinyl; morpholino; etc.

[0090] As the "substituents" in the "heterocyclic groups which may be substituted", those exemplified as the "substituents" in the above "5- to 10-membered aromatic heterocyclic groups which may be substituted" can be used. The

number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0091] Examples of the "C_{1-6} alkyl" represented by R^4 include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.

[0092] Examples of the "nitrogen-containing heterocyclic ring" in the "nitrogen-containing heterocyclic ring which may be substituted" formed by R^3 and R^4 together with the adjacent nitrogen atom include a 5- to 7-membered nitrogen-containing heterocyclic ring which contains at least one nitrogen atom in addition to carbon atoms and may contain 1 to 3 hetero atoms selected from nitrogen, sulfur and oxygen atoms. The "nitrogen-containing heterocyclic rings" are preferably piperidine, morpholine, thiomorpholine, piperazine, pyrrolidine, etc.

[0093] As the "substituents" in the "nitrogen-containing heterocyclic ring which may be substituted", those exemplified as the "substituents" in the above "5- to 10-membered aromatic heterocyclic groups which may be substituted" can be used. The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0094] The "acyl" is preferably formyl, carboxy, carbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl (e.g. acetyl, etc.), C_{1-6} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), C_{6-14} aryl-carbonyl which may be substituted (e.g. benzoyl, 1-naphthoyl, 2-naphthoyl, etc.), C_{6-14} aryloxy-carbonyl which may be substituted (e.g. phenyloxycarbonyl, 1-naphthyloxycarbonyl, 2-naphthyloxycarbonyl, etc.), C_{7-19} aralkyloxy-carbonyl which may be substituted (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.), a 5- to 6-membered heterocyclic ring-carbonyl which may be substituted (e.g. nicotinoyl, etc.), mono-C_{1-6} alkyl-carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl, etc.), C_{6-14} aryl-carbamoyl which may be substituted (e.g. phenylcarbamoyl, 4-methoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, etc.), aromatic heterocyclic ring-carbamoyl which may be substituted (e.g. 2-pyridinylcarbamoyl, 2-quinolinylcarbamoyl etc.), optionally halogenated C_{1-6} alkylsulfonyl (e.g. methylsulfonyl, etc.), C_{6-14} arylsulfonyl which may be substituted (e.g. phenylsulfonyl etc.), etc.

[0095] Here, as the "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{1-6} alkylsulfonyl", those exemplified as the "substituents" in the above "C_{7-19} aralkyl which may be substituted" can be used, respectively.

[0096] As the "C_{6-14} aryl-carbonyl which may be substituted", those exemplified as the "substituents" in the above "5- to 7-membered saturated cyclic amino which may be substituted" can be used.

[0097] As the "C_{6-14} aryloxy-carbonyl which may be substituted", "C_{7-19} aralkyloxy-carbonyl which may be substituted", "5- to 6-membered heterocyclic ring-carbonyl which may be substituted", "aromatic heterocyclic ring-carbamoyl which may be substituted" and "C_{6-14} arylsulfonyl which may be substituted", those exemplified as the "substituents" in the above "hydrocarbon groups which may be substituted" can be used, respectively.

[0098] As the "C_{6-14} aryl-carbamoyl which may be substituted", those exemplified as the "substituents" in the above "cyclic group which may be substituted" can be used.

[0099] Examples of the above "acylamino" include amino which is substituted by 1 or 2 of the above "acyl". Preferably, acylamino of the formulas: -NR^5-COR^6, -NR^5-$COOR^{6a}$, -NR^5-SO_2R^{6a}, -NR^5-$CONR^{6a}R^{6b}$, -$PO(-OR^5)$-OR^6, or -PO_2-R^6 wherein R^5 is hydrogen atom or C_{1-6} alkyl; R^6 is as defined with respect to the above R^3; R^{6a} is as defined with respect to the above R^{3a}; and R^{6b} is as defined with respect to R^4], etc., can be mentioned.

[0100] As the "C_{1-6} alkyl" represented by R^5, the same one as the "C_{1-6} alkyl" for the above R^4 can be mentioned.

[0101] The "acylamino" is preferably formylamino, optionally halogenated C_{1-6} alkyl-carboxamide (e.g. methylcarboxamide, trifluoromethylcarboxamide, etc.), C_{6-14} aryl-carboxamide which may be substituted (e.g. phenylcarboxamide, 2-methoxyphenylcarboxamide, 4-methoxyphenylcarboxamide, etc.), N-(C_{6-14} aryl-carbonyl which may be substituted)-N-C_{1-6} alkylamino (e.g. N-4-methoxybenzoyl-N-methylamino, etc.), C_{7-19} aralkyl-carboxamide which may be substituted (e.g. benzylcarboxamide, etc.), aromatic heterocyclic ring-carboxamide which may be substituted (e.g. benzothiophen-2-ylcarboxamide, etc.), optionally halogenated C_{1-6} alkoxy-carboxamide (e.g. methoxycarboxamide, ethoxycarboxamide, propoxycarboxamide, butoxycarboxamide, etc.), C_{6-14} arylamino-carbonylamino which may be substituted (e.g. phenylaminocarbonylamino, etc.), optionally halogenated C_{1-6} alkylsulfonylamino (e.g. methylsulfonylamino, trifluoromethylsulfonylamino, ethylsulfonylamino, etc.), C_{6-14} arylsulfonylamino which may be substituted (e.g. 4-methoxyphenylsulfonylamino, etc.), etc.

[0102] Here, as the "substituents" in the "C_{6-14} aryl-carboxamide which may be substituted", "N-(C_{6-14} aryl-carbonyl which may be substituted)-N-C_{1-6} arylkylamino", "C_{7-19} aralkyl-carboxamide which may be substituted", "aromatic heterocyclic ring-carboxamide which may be substituted", "C_{6-14} arylamino-carbonylamino which may be substituted" and "C_{6-14} arylsulfonylamino which may be substituted", those exemplified as the "substituents" in the above "C_{7-19} aralkyl which may be subsituted" can be mentioned. The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0103] Examples of the above "acyloxy" include oxy substituted by one of the above "acyl". Preferably, acyloxy of the formulas: -O-COR^7, -O-$COOR^7$, -O-$CONHR^7$, -$PO(OH)$-OR^7 or -PO_2-R^7 wherein R^7 is as defined with respect to the above R^3, etc., can be mentioned.

[0104] The "acyloxy" is preferably optionally halogenated C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propanoyloxy, etc.), C_{6-14} aryl-carbonyloxy which may be substituted (e.g. benzoyloxy, 4-methoxybenzoyloxy, etc.), optionally halogenated C_{1-6} alkoxy-carbonyloxy (e.g. methoxycarbonyloxy, trifluoromethoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g. methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g. dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), C_{6-14} aryl-carbamoyloxy which may be substituted (e.g. phenylcarbamoyloxy, naphthylcarbamoyloxy, etc.), nicotinoyloxy, etc.

[0105] As the "substituents" in "C_{6-14} aryl-carbonyloxy which may be substituted" and "C_{6-14} aryl-carbamoyloxy which may be substituted", those exemplified as the "substituents" in the above "C_{7-19} aralkyl which may be substituted" can be mentioned. The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0106] Examples of the "5- to 7-membered non-aromatic heterocyclic groups" in the "5- to 7-membered non-aromatic heterocyclic groups which may be substituted" which is the "substituents" in "cyclic group which may be substituted" represented by R and Ar^1, include 4,5-dihydro-1,3-oxazol-2-yl, 4,5-dihydro-1,3-thiazol-2-yl, 4,5-dihydro-1H-2-imidazolyl, etc. As the "substituents" in the "5- to 7-membered non-aromatic heterocyclic groups which may be substituted", those exemplified as the "substituents" in the above "5- to 7-membered saturated cyclic amino which may be substituted" can be used.

[0107] As the "acyl", "acyloxy" and "acylamino", which are the "substituents" in the "cyclic group which may be substituted" represented by R and Ar^1, those exemplified as the "substituents" in the above "5- to 10-membered aromatic heterocyclic groups which may be substituted" can be used.

[0108] The "substituents" in the "cyclic group which may be substituted" for R and Ar^1 are preferably a halogen atom (preferably fluorine, chlorine and bromine, etc.); nitro; C_{1-3} alkylenedioxy (preferably methylenedioxy, etc.); optionally halogenated C_{1-6} alkyl (preferably, methyl, ethyl, propyl, trifluoromethyl, tert-butyl, etc.); hydroxy-C_{1-6} alkyl (preferably hydroxymethyl, etc.); optionally halogenated C_{3-6} cycloalkyl (preferably cyclohexyl, etc.); optionally halogenated C_{1-6} alkoxy (preferably methoxy, ethoxy, etc.); optionally halogenated C_{1-6} alkylthio (preferably methylthio, etc.); hydroxy; C_{7-19} aralkyloxy which may be substituted (preferably benzyloxy, 4-methoxybenzyloxy, 3-methoxybenzyloxy, 4-fluorobenzyloxy, 4-methylthiobenzyloxy, 4-ethylbenzyloxy, etc.); C_{6-14} aryloxy which may be substituted (preferably phenyloxy, etc.); amino; mono-C_{1-6} alkylamino (preferably methylamino, etc.); di-C_{1-6} alkylamino (preferably dimethylamino, etc.); 5- to 7-membered saturated cyclic amino which may be substituted and may be condensed with a benzene ring (preferably 1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl, etc.); 5- to 7-membered non-aromatic heterocyclic groups which may be substituted (preferably 4,5-dihydro-1,3-oxazol-2-yl, etc.); formyl; carboxy; C_{6-14} aryl-carbonyl which may be substituted (preferably benzoyl, etc.); C_{6-14} aryl-carbamoyl which may be substituted (preferably, phenylcarbamoyl, 4-methoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, etc.); aromatic heterocyclic ring-carbamoyl which may be substituted (preferably 2-pyridinylcarbamoyl, 2-quinolinylcarbamoyl, etc.); C_{1-6} alkoxy-carbonyl (preferably methoxycarbonyl, ethoxycarbonyl, etc.); optionally halogenated C_{1-6} alkyl-carboxamide (preferably methylcarboxamide, trifluoromethylcarboxamide, etc.); C_{6-14} aryl-carboxamide which may be substituted (preferably phenylcarboxamide, 2-methoxyphenylcarboxamide, 4-methoxyphenylcarboxamide, etc.); C_{7-19} aralkyl-carboxamide which may be substituted (preferably benzylcarboxamide, etc.); aromatic heterocyclic ring-carboxamide which may be substituted (preferably benzothiophen-2-ylcarboxamide, etc.); N-(C_{6-14} aryl-carbonyl which may be substituted)-N-C_{1-6} alkylamino (preferably N-4-methoxybenzoyl-N-methylamino, etc.); C_{6-14} arylamino-carbonylamino which may be substituted (preferably phenylaminocarbonylamino, etc.); C_{6-14} arylsulfonylamino which may be substituted (preferably 4-methoxyphenylsulfonylamino, etc.); C_{6-14} aryl-carbonyloxy which may be substituted (preferably 4-methoxybenzoyloxy, etc.); oxo; etc.

[0109] When the "cyclic group" in the "cyclic group which may be substituted" represented by R and Ar^1 is a non-aromatic cyclic hydrocarbon group or a non-aromatic heterocyclic group, C_{6-14} aryl which may be substituted (preferably phenyl), etc., can be used as a preferred substituent.

[0110] More preferably, the "substituent" of the "cyclic group which may be substituted" represented by R and Ar^1 is a halogen atom (preferably chlorine, etc.), C_{1-6} alkyl (preferably methyl, etc.), C_{7-19} aralkyloxy which may be substituted with C_{1-6} alkoxy (preferably methoxybenzyloxy, etc.), etc.

[0111] R and Ar^1 are preferably phenyl, biphenylyl (preferably 4-biphenylyl), phenyl-pyridyl (preferably 6-phenyl-3-pyridyl, 5-phenyl-2-pyridyl), phenyl-furyl (preferably 5-phenyl-2-furyl), phenyl-isoxazole (preferably 3-phenyl-isoxazol-5-yl), diphenyl-oxazole (preferably 2,4-diphenyl-1,3-oxazol-5-yl), pyridyl-phenyl (preferably 4-(4-pyridyl)phenyl), phenyl-pyrimidinyl (preferably 2-phenyl-5-pyrimidinyl), benzofuranyl-phenyl (preferably 4-(2-benzofuranyl)phenyl), furyl-phenyl (preferably 4-(2-furyl)phenyl), pyrrolyl (preferably 1-pyrrolyl) or naphthyl; each of which may have 1 or 2 substituents selected from the group consisting of a halogen atom (preferably fluorine, chlorine and bromine, etc.); nitro; C_{1-3} alkylenedioxy (preferably methylenedioxy, etc.); optionally halogenated C_{1-6} alkyl (preferably, methyl, ethyl, propyl, trifluoromethyl, tert-butyl, etc.); hydroxy-C_{1-6} alkyl (preferably hydroxymethyl, etc.); optionally halogenated C_{3-6} cycloalkyl (preferably cyclohexyl, etc.); optionally halogenated C_{1-6} alkoxy (preferably methoxy, ethoxy, etc.); optionally halogenated C_{1-6} alkylthio (preferably methylthio, etc.); hydroxy; C_{7-19} aralkyloxy which may be substituted (preferably benzyloxy, 4-methoxybenzyloxy, 3-methoxybenzyloxy, 4-fluorobenzyloxy, 4-methylthiobenzyloxy, 4-ethylbenzyloxy,

etc.); C_{6-14} aryloxy which may be substituted (preferably phenyloxy, etc.); amino; mono-C_{1-6} alkylamino (preferably methylamino, etc.); di-C_{1-6} alkylamino (preferably dimethylamino, etc.); 5- to 7-membered saturated cyclic amino which may be substituted and may be condensed with a benzene ring (preferably 1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl, etc.); 5- to 7-membered non-aromatic heterocyclic groups which may be substituted (preferably 4,5-dihydro-1,3-oxazol-2-yl, etc.); formyl; carboxy; C_{6-14} aryl-carbonyl which may be substituted (preferably benzoyl, etc.); C_{6-14} aryl-carbamoyl which may be substituted (preferably, phenylcarbamoyl, 4-methoxyphenylcarbamoyl, 3,4-dimethoxyphenylcarbamoyl, etc.); aromatic heterocyclic ring-carbamoyl which may be substituted (preferably 2-pyridinylcarbamoyl, 2-quinolinylcarbamoyl, etc.); C_{1-6} alkoxy-carbonyl (preferably methoxycarbonyl, ethoxycarbonyl, etc.); optionally halogenated C_{1-6} alkyl-carboxamide (preferably methylcarboxamide, trifluoromethylcarboxamide, etc.); C_{6-14} aryl-carboxamide which may be substituted (preferably phenylcarboxamide, 2-methoxyphenylcarboxamide, 4-methoxyphenylcarboxamide, etc.); C_{7-19} aralkyl-carboxamide which may be substituted (preferably benzylcarboxamide, etc.); aromatic heterocyclic ring-carboxamide which may be substituted (preferably benzothiophen-2-ylcarboxamide, etc.); N-(C_{6-14} aryl-carbonyl which may be substituted)-N-C_{1-6} alkylamino (preferably N-4-methoxybenzoyl-N-methylamino, etc.); C_{6-14} arylamino-carbonylamino which may be substituted (preferably phenylaminocarbonylamino, etc.); C_{6-14} arylsulfonylamino which may be substituted (preferably 4-methoxyphenylsulfonylamino, etc.); C_{6-14} aryl-carbonyloxy which may be substituted (preferably 4-methoxybenzoyloxy, etc.); oxo; etc.

[0112] Further, preferred examples of R and Ar^1 include piperidino, piperazinyl, pyrrolidinyl, etc.; each of which may have 1 or 2 substituents selected from the group consisting of oxo and C_{6-14} aryl which may be substituted (preferably phenyl).

[0113] Examples of the halogen atom represented by R include fluorine, chlorine, bromine, iodine, etc. Among them, fluorine is preferred.

[0114] The "spacer having a main chain of 1 to 10 atoms" represented by X means a space in which 1 to 10 atoms are linked. Here, the "number of atoms in the main chain" is counted so that the number of atoms in the main chain is minimum. For example, the number of atoms of 1,2-cyclopentylene is counted as 2, and the number of atoms of 1,3-cyclopentylene is counted as 3.

[0115] Examples of the "spacer having a main chain of 1 to 10 atoms" include a bivalent group consisting of 1 to 5 members selected from -O-, -S-, -CO-, -SO-, $-SO_2-$, $-NR^8-$ (R^8 is hydrogen atom, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkyl-carbonyl, optionally halogenated C_{1-6} alkylsulfonyl), bivalent C_{1-6} non-cyclic hydrocarbon groups which may be substituted, and bivalent C_{5-8} monocyclic non-aromatic hydrocarbon groups, and the like.

[0116] Here, as the "optionally halogenated C_{1-6} alkyl", those exemplified as the "substituents" in the above "cyclic group which may be substituted" can be used.

[0117] As the "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{1-6} alkylsulfonyl", those exemplified as the "substituents" in the above "C_{7-19} aralkyl which may be substituted" can be used, respectively.

[0118] Examples of the "bivalent C_{1-6} non-cyclic hydrocarbon groups" in the "bivalent C_{1-6} non-cyclic hydrocarbon groups which may be substituted" include

(1) C_{1-6} alkylene (e.g. $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH_2-CH(CH_3)-$, $-(CH(CH_3))_2-$, $-(CH_2)_2C(CH_3)_2-$, $-(CH_2)_3C(CH_3)_2-$, etc.);
(2) C_{2-6} alkenylene (e.g. -CH=CH-, $-CH_2-CH=CH-$, -CH=CH-CH_2-, -CH=CH-CH_2-CH_2-, $-CH_2-CF=CH-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, -CH=CH-CH=CH-, -CH=CH-$CH_2-CH_2-CH_2-$, etc.);
(3) C_{2-6} alkynylene (e.g. $-C\equiv C-$, $-CH_2-C\equiv C-$, $-C\equiv C-CH_2-$, $-CH_2-C\equiv C-CH_2-CH_2-$, etc.); etc.

[0119] Examples of the "substituent" in the "bivalent C_{1-6} non-cyclic hydrocarbon groups which may be substituted" include halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), hydroxy, nitro, cyano, optionally halogenated C_{1-6} alkoxy, optionally halogenated C_{1-6} alkylthio, amino, mono-C_{1-6} alkylamino (e.g., methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-C_{1-6} alkylamino (e.g., dimethylamino, diethylamino, dipropylamino, dibutylamino, ethylmethylamino, etc.), formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), optionally halogenated C_{1-6} alkylsulfonyl, etc. The number of substituents is, for example, 1 to 5, preferably 1 to 3.

[0120] Here, as the "optionally halogenated C_{1-6} alkoxy" and "optionally halogenated C_{1-6} alkylthio", those exemplified as the "substituent" in the above "cyclic group which may be substituted" can be used, respectively.

[0121] As the "optionally halogenated C_{1-6} alkyl-carbonyl" and "optionally halogenated C_{1-6} alkylsulfonyl", those exemplified as the "substituent" in the above "C_{7-19} aralkyl which may be substituted" can be used.

[0122] Preferably, the "substituent" in the "bivalent C_{1-6} non-aromatic hydrocarbon group which may be substituted" is a halogen atom (e.g., fluorine, chlorine, bromine, iodine, etc.), hydroxy, etc.

[0123] As the "bivalent C_{5-8} monocyclic non-aromatic hydrocarbon groups", for example, bivalent groups formed by removing an optional two hydrogen atoms from C_{5-8} cycloalkane or C_{5-8} cycloalkene, can be mentioned. Specific examples include 1,2-cyclopentylene; 1,3-cyclopentylene; 1,2-cyclohexylene; 1,3-cyclohexylene; 1,4-cyclohexylene;

1,2-cycloheptylene; 1,3-cycloheptylene; 1,4-cycloheptylene; 3-cyclohexen-1,4-ylene; 3-cyclohexen-1,2-ylene; 2,5-cyclohexadien-1,4-ylene, etc. Especially, C_{5-8} cycloalkylene is preferable.

[0124] As the "spacer having a main chain of 1 to 6 atoms" represented by Y, among the above "spacer having a main chain of 1 to 10 atoms" represented by X, that whose main chain has 1 to 6 atoms can be mentioned.

[0125] The "spacer" represented by X and Y is preferably the "spacer having a main chain of 1 to 6 atoms", more preferably a bivalent group consisting of 1 to 3 members selected from -O-, -S-, -CO-, -SO-, $-SO_2-$, $-NR^8-$ (R^8 is as defined above) and bivalent C_{1-6} non-cyclic hydrocarbon group which may be substituted.

[0126] Preferred examples of the "spacer having a main chain of 1 to 6 atoms" include

(1) C_{1-6} alkylene (e.g. $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH(OH)-(CH_2)_2-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CHCH_3-$, $-C(CH_3)_2-$, $-CH_2-CH(CH_3)-$, $-CH(CF_3)-$, $-(CH(CH_3))_2-$, $-(CF_2)_2-$, $-(CH_2)_2C(CH_3)_2-$, $-(CH_2)_3C(CH_3)_2-$, etc.) which may be substituted (preferably with halogen atom, hydroxy, etc.);

(2) C_{2-6} alkenylene (e.g. -CH=CH-, $-CH_2-CH=CH-$, $-CH=CH-CH_2-$, $-CH=CH-CH_2-CH_2-$, $-CH_2-CF=CH-$, $-C(CH_3)_2-CH=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-$, $-CH=CH-CH=CH-$, $-CH=CH-CH_2-CH_2-CH_2-$, etc.) which may be substituted (preferably with halogen atom, hydroxy, etc.);

(3) C_{2-6} alkynylene (e.g. $-C\equiv C-$, $-CH_2-C\equiv C-$, $-C\equiv C-CH_2-$, $-CH_2-C\equiv C-CH_2-CH_2-$, etc.) which may be substituted (preferably with halogen atom, hydroxy, etc.);

(4) $-(CH_2)_{w1}O(CH_2)_{w2}-$, $-(CH_2)_{w1}S(CH_2)_{w2}-$, $-(CH_2)_{w1}CO(CH_2)_{w2}-$, $-(CH_2)_{w1}SO(CH_2)_{w2}-$, $-(CH_2)_{w1}SO_2(CH_2)_{w2}-$, $-(CH_2)_{w1}NR^8(CH_2)_{w2}-$;

(5) $-(CH_2)_{w3}CO-$, $-(CH_2)_{w3}CONR^8(CH_2)_{w4}-$, $-(CH_2)_{w3}NR^8CO(CH_2)_{w4}-$, $-(CH_2)_{w3}SO_2NR^8(CH_2)_{w4}-$, $-(CH_2)_{w3}NR^8SO_2(CH_2)_{w4}-$, $-(CH_2)_{w3}COO(CH_2)_{w4}-$;

(6) $-(CH_2)_{w5}NR^8CO-$, $-(CH_2)_{w5}NR^8CONR^{8b}(CH_2)_{w6}-$, $-(CH_2)_{w5}CH=CH(CH_2)_{w6}CO-$;

(7) $-O(CH_2)_{w7}CO-$, $-CO(CH_2)_{w7}CO-$, $-S(CH_2)_{w7}CO-$, $-SO(CH_2)_{w7}CO-$, $-SO_2(CH_2)_{w7}CO-$, $-NR^8(CH_2)_{w7}CO-$, -COCH=CHCO-;

(8) $-NR^8CO(CH_2)_{w8}CO-$, $-CONR^8(CH_2)_{w8}CO-$;

wherein R^8 is as defined above; R^{8b} is as defined with respect to R^8; w1 and w2 is an integer of 0 to 5, and w1 + w2 is 0 to 5; w3 and w4 is an integer of 0 to 4, and w3 + w4 is 0 to 4; w5 and w6 is an integer of 0 to 3, and w5 + w6 is 0 to 3; w7 is an integer of 0 to 4; and w8 is an integer of 0 to 3, etc.

[0127] The "spacer having a main chain of 1 to 10 atoms" represented by X is more preferably $-(CH_2)_{w1}O(CH_2)_{w2}-$, $CONR^8-$, $-NR^8CO-$, $-(CH_2)_{w3}CO-$, $-(CH_2)_{w5}NR^8CO-$, -CO-, $-(CH_2)_{w1}CO(CH_2)_{w2}-$, (the symbols are as defined above), C_{1-3} alkylene (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2-CH(CH_3)-$, etc.) which may be substituted (preferably with halogen atom, hydroxy, etc.), C_{2-6} alkenylene (preferably $-CH=CH-CH_2-$, etc.) which may be substituted (preferably with halogen atom, hydroxy, etc.), C_{2-6} alkynylene (preferably $-C\equiv C-CH_2-$, etc.) which may be substituted (preferably with halogen atom, hydroxy, etc.), $-(CH_2)_{w1}SO_2(CH_2)_{w2}-$ (the symbols are as defined above), etc., in particular, -CO-.

[0128] More preferably, the "spacer having a main chain of 1 to 6 atoms" represented by Y is $-(CH_2)_{w1}O(CH_2)_{w2}-$ (the symbols are as defined above) (preferably $-O(CH_2)_{w2}-$) (e.g., $-O(CH_2)_3-$, etc.), C_{1-3} alkylene (e.g., $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH(OH)-(CH_2)_2-$, etc.) which may be substituted (preferably with halogen atom, hydroxy, etc.), C_{2-6} alkenylene (e.g., -CH=CH-, $-CH_2-CH=CH-$, $-CH=CH-CH_2-$, -CH=CH-CH2-CH2-, etc.) which may be substituted (preferably with halogen atom, hydroxy, etc.),$-(CH_2)_{w3}CONH(CH_2)_{w4}-$, $-(CH_2)_{w3}COO(CH_2)_{w4}-$ (the symbols are as defined above), $-(CH_2)_{w1}CO(CH_2)_{w2}-$ (the symbols are as defined above), (e.g., $-CO(CH_2)_2-$, $-CO(CH_2)_3-$, $-(CH_2)_2CO-$, $-(CH_2)_3CO-$, etc.), $-CO(CH_2)_{w7}CO-$ (the symbols are as defined above) (e.g., $-CO(CH_2)_2CO-$, $-CO(CH_2)_3CO-$, etc.), -COCH=CHCO-, $-O(CH_2)_{w7}CO-$ (the symbols are as defined above) (e.g., $-O(CH_2)_2CO-$, etc.), $-CONP^8(CH_2)_{w8}CO-$ (the symbols are as defined above) (e.g., $-CONHCH_2CO-$), etc.

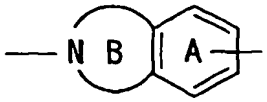
[0129] In the formula (I"), as the "spacer having a main chain of 1 to 5 atoms" represented by Ya, among the above "spacer having a main chain of 1 to 10 atoms" represented by X, that whose main chain has 1 to 5 atoms can be mentioned. Ya is preferably $-(CH_2)_{w1}O(CH_2)_{w2}-$ (the symbols are as defined above) (preferably $-CO(CH_2)_2-$), etc.

[0130] In the formula (I'"), the "spacer having a main chain of 1 to 6 atoms" is the same as the above Y.

[0131] The particularly preferred X is a bond, $-(CH_2)_{w1}CO(CH_2)_{w2}-$ (the symbols are as defined above), C_{1-3} alkylene (preferably $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2-CH(CH_3)-$, etc.), C_{2-6} alkenylene (preferably $-CH=CH-CH_2-$, etc.), C_{2-6} alkynylene (e.g., $-C\equiv C-CH_2-$, etc.), etc.

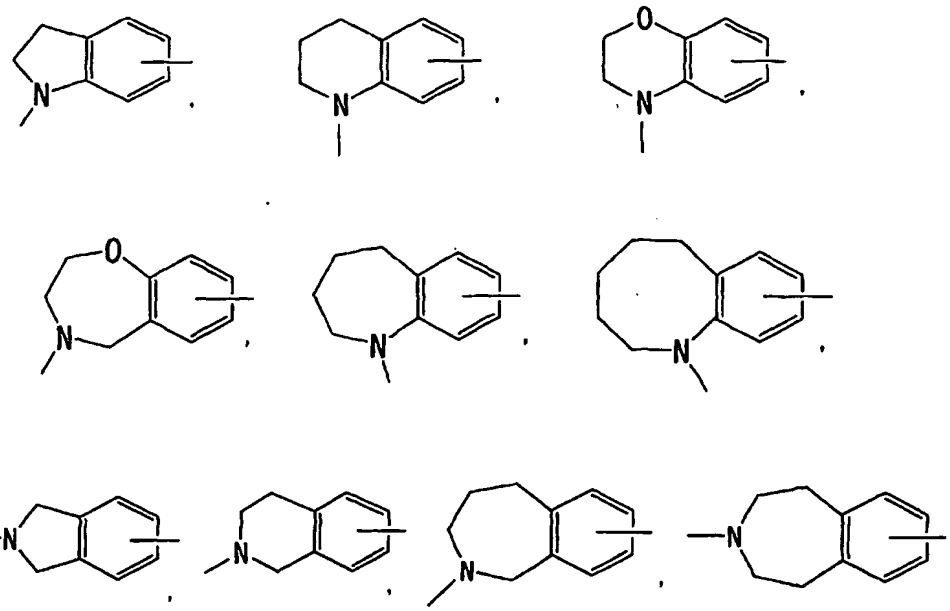
[0132] The particularly preferred Y is $-(CH_2)_{w1}O(CH_2)_{w2}-$ (the symbols are as defined above) (preferably $-O(CH_2)_{w2}-$, more preferably $-O(CH_2)_3-$, etc.), C_{1-3} alkylene which may be substituted with hydroxy group (preferably $-(CH_2)_3-$, $-CH(OH)-(CH_2)_2-$, etc.), C_{2-6} alkenylene (preferably $-CH=CH-CH_2-$, $-CH=CH-CH_2-CH_2-$, etc.), $-(CH_2)_{w1}CO(CH_2)_{w2}-$ (the symbols are as defined above) (preferably $-CO(CH_2)_3-$, etc.), $-CO(CH_2)_{w7}CO-$ (the symbols are as defined above) (preferably $-CO(CH_2)_2CO-$, etc.), etc.

[0133] The group represented by the formula:

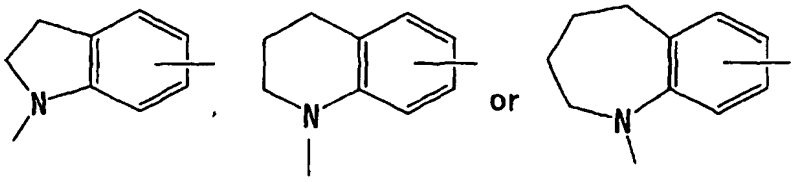


wherein the symbols are as defined above, and the group represented by the formula:

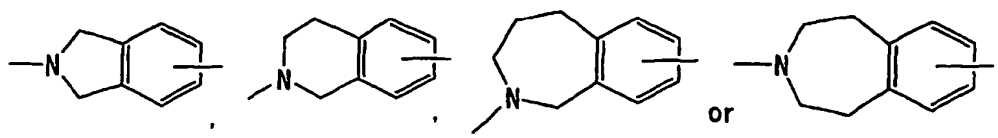
wherein the symbols are as defined above, are preferably



and the like. Among them,



etc., is preferred. Further,



etc., is also preferred.

[0134] As the "substituents" in the "benzene ring" represented by ring A and the "5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring" represented by ring B, those exemplified as the "substituents" in the "cyclic group which may be substituted" represented by the above R and Ar^1 can be used.

[0135] The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0136] The substituents on ring A and ring B are preferably oxo, C_{6-14} aryl which may be substituted (preferably with C_{1-6} alkoxy), etc.

[0137] As the "hydrocarbon groups which may be substituted" represented by R^1 and R^2, those exemplified as the above R^3 can be used.

[0138] The "hydrocarbon groups which may be substituted" are preferably "C_{1-6} alkyl which may be substituted", C_{2-6} alkynyl (e.g., ethynyl, etc.), C_{3-6} cycloalkyl (e.g., cyclopropyl, cyclohexyl, etc.), C_{6-14} aryl (e.g., phenyl, naphthyl, etc.), dihydroindene, etc. Among them, "C_{1-6} alkyl which may be substituted" is preferred, in particular, "C_{1-6} alkyl" is preferred.

[0139] Here, examples of the "C_{1-6} alkyl" in the "C_{1-6} alkyl which may be substituted" include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc. Especially, methyl, ethyl, propyl, etc. are preferred.

[0140] Examples of the "substituents" in the "C_{1-6} alkyl which may be substituted" include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-3} alkylenedioxy (e.g. methylenedioxy, ethylenedioxy etc.), nitro, cyano, optionally halogenated C_{3-6} cycloalkyl (e.g., cyclohexyl, etc.), optionally halogenated C_{1-6} alkoxy (e.g., methoxy, isopropoxy, etc.), optionally halogenated C_{1-6} alkylthio (e.g., methylthio, etc.), hydroxy, amino, mono-C_{1-6} alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino, etc.), di-(C_{1-6} alkyl which may be substituted with hydroxy)amino (e.g. dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, ethylmethylamino, di(hydroxyethyl) amino, etc.), C_{6-14} arylamino which may be substituted with one to three C_{1-6} alkyl (e.g., phenylamino, 2,6-dimethylphenylamino, etc.), N-C_{1-6} alkyl-N-(C_{6-14} aryl which may be substituted with C_{1-6} alkyl)amino (e.g., N-methyl-N-phenylamino, N-ethyl-N-(methylphenyl)amino, etc.), 5- or 6-membered monocyclic aromatic heterocyclic ring amino which may be substituted with nitro (e.g., nitropyridylamino, etc.), 5- to 8-membered monocyclic non-aromatic heterocyclic group (e.g., tetrahydrofuryl, pyrrolidinyl, oxopyrrolidinyl, piperidinyl, methylpiperidinyl, morpholinyl, methylpiperazinyl, etc.), formyl, carboxy, carbamoyl, thiocarbamoyl, optionally halogenated C_{1-6} alkyl-carbonyl, C_{1-6} alkoxy-carbonyl (e. g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert-butoxycarbonyl, etc.), mono-C_{1-6} alkyl-carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, etc.), di-C_{1-6} alkyl-carbamoyl (e.g. dimethylcarbamoyl, diethylcarbamoyl, ethylmethylcarbamoyl etc.), optionally halogenated C_{1-6} alkylsulfonyl, formylamino, optionally halogenated C_{1-6} alkyl-carboxamide, C_{1-6} alkoxy-carboxamide (e.g. methoxycarboxamide, ethoxycarboxamide, propoxycarboxamide, butoxycarboxamide, etc.), C_{1-6} alkylsulfonylamino (e.g. methylsulfonylamino, ethylsulfonylamino, etc.), C_{1-6} alkyl-carbonyloxy (e.g. acetoxy, propanoyloxy, etc.), C_{1-6} alkoxy-carbonyloxy (e.g. methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.), mono-C_{1-6} alkyl-carbamoyloxy (e.g. methylcarbamoyloxy, ethylcarbamoyloxy, etc.), di-C_{1-6} alkyl-carbamoyloxy (e.g. dimethylcarbamoyloxy, diethylcarbamoyloxy, etc.), aromatic groups which may be substituted, optionally halogenated C_{8-19} aryloxy (e.g., phenoxy, chlorophenyloxy, etc.), etc. The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0141] Here, as the "optionally halogenated C_{3-6} cycloalkyl", "optionally halogenated C_{1-6} alkoxy" and "optionally halogenated C_{1-6} alkylthio", those exemplified as the "substituents" in the above "cyclic group which may be substituted" can be used.

[0142] As the "optionally halogenated C_{1-6} alkyl-carbonyl", "optionally halogenated C_{1-6} alkylsulfonyl" and "optionally halogenated C_{1-6} alkyl-carboxamide", those exemplified as the "substituents" in the above "C_{7-19} aralkyl which may be substituted" can be used.

[0143] As the "substituents" and "aromatic groups" in the "aromatic groups which may be substituted", those exemplified as the "substituents" and "aromatic groups" in the "cyclic group which may be substituted" represented by the above R can be used. The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0144] The "aromatic groups" are preferably phenyl, naphthyl, furyl, pyridyl, imidazoly, indolyl, etc. And, the "substit-

uents" are preferably C_{1-3} alkylenedioxy (e.g., methylenedioxy, etc.), optionally halogenated C_{1-6} alkyl (e.g., trifluoromethyl, etc.), optionally halogenated C_{1-6} alkoxy (e.g., methoxy, etc.), a halogen atom (e.g., chlorine, etc.), etc.

[0145] As the "heterocyclic group which may be substituted" represented by R^1 and R^2, those exemplified as the above R^3 can be used.

[0146] The "heterocyclic group" in the "heterocyclic group which may be substituted" is preferably a 5- to 10-membered non-aromatic heterocyclic group, more preferably pyrrolidinyl, piperidinyl, etc. Further, the "substituent" in the "heterocyclic group which may be substituted" is preferably optionally halogenated C_{1-6} alkyl (e.g., methyl, etc.), C_{7-19} aralkyl (e.g., benzyl, etc.), etc. The number of the substituents is, for example, 1 to 5.

[0147] Examples of the "nitrogen-containing heterocyclic rings" in the "nitrogen-containing heterocyclic rings which may be substituted" formed by R^1 and R^2 together with the adjacent nitrogen atom include 3- to 10-membered (preferably 3- to 8-membered) nitrogen-containing heterocyclic rings which contain at least one nitrogen atom in addition to carbon atoms, and which may further contain 1 to 3 hetero atoms selected from nitrogen, sulfur and oxygen atoms. Specific examples include aziridine, azetidine, morpholine, thiomorpholine, piperidine, piperazine, pyrrolidine, hexamethyleneimine, heptamethyleneimine, hexahydropyrimidine, 1,4-diazepan, dihydroisoquinoline, and their unsaturated cyclic amines (e.g. 1,2,5,6-tetrahydropyridine, 1,4-diazepin, octahydroisoquinoline, etc.), etc. can be mentioned. Especially, morpholine, piperidine, piperazine, pyrrolidine, etc., are preferred.

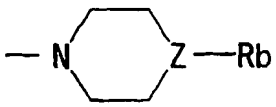
[0148] As the "substituents" in the "nitrogen-containing heterocyclic rings which may be substituted", for example, those exemplified as the "substituents" in the above "5- to 7-membered saturated cyclic amino which may be substituted" can be used. The number of substituents is, for example, 1 to 5, preferably 1 to 3. When the number of substituents is 2 or more, each substituents can be the same or different.

[0149] The "substituents" are preferably hydroxy; optionally halogenated C_{1-6} alkyl (preferably methyl, ethyl, etc.); C_{6-14} aryl (e.g., phenyl, naphthyl, etc.) which may have 1 to 3 substituents selected from halogen atom, optionally halogenated C_{1-6} alkyl and optionally substituted C_{1-6} alkoxy; carbamoyl; hydroxy-C_{1-6} alkyl; C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl (e.g., ethoxycarbonylmethyl, etc.); C_{7-19} aralkyl (e.g., benzyl, diphenylmethyl, etc.) which may be substituted with C_{1-3} alkylenedioxy (e.g., methylenedioxy, etc.); 5- to 10-membered aromatic heterocyclic group (preferably pyridyl, pyrimidinyl, etc.); 5- to 8-monocyclic non-aromatic heterocyclic group (e.g., pyrrolidinyl, piperidinyl, etc.); C_{8-19} arylalkenyl (e.g., 3-phenyl-2-prop-2-enyl, etc.); C_{1-6} alkyl-carboxamide (e.g., methylcarboxamide, etc.); (N-C_{1-6} alkyl)-C_{1-6} alkyl-carboxamide (e.g., (N-ethyl)methylcarboxamide, etc.); di-C_{1-6} alkylamino (e.g., dimethylamino, etc.), 5- to 8-membered monocyclic non-aromatic heterocyclic group-C_{1-6} alkyl (e.g., pyrrolidinylmethyl, etc.); C_{6-14} aryl-amino-C_{1-6} alkyl (e.g., 2,6-dimethylphenylaminomethyl, etc.) substituted with 1 to 3 C_{1-6} alkyl; etc.

[0150] Preferably, R^1 and R^2, together with the adjacent nitrogen atom, form a nitrogen-containing heterocyclic ring which may be substituted.

[0151] In particular, R^1 and R^2, together with the adjacent nitrogen atom, form piperidino, pyrrolidin-1-yl, etc.

[0152] The "nitrogen-containing heterocyclic rings which may be substituted" formed by R^1 and R^2 together with the adjacent nitrogen atom is preferably



wherein the symbols are as defined above.

[0153] Here, as the "hydrocarbon group which may be substituted" represented by Rb, those exemplified as the above R^3 can be mentioned. Preferably, Rb is a hydrocarbon group which may be substituted and specific examples thereof include optionally halogenated C_{1-6} alkyl (preferably methyl, ethyl, etc.); C_{6-14} aryl (e.g., phenyl, naphthyl, etc.) which may have 1 to 3 substituents selected from halogen atom (e.g., fluorine, chlorine, etc.), optionally halogenated C_{1-6} alkyl (e.g., methyl, etc.) and optionally substituted C_{1-6} alkoxy (e.g., methoxy, etc.); hydroxy-C_{1-6} alkyl; C_{1-6} alkoxy-carbonyl-C_{1-6} alkyl (e.g., ethoxycarbonylmethyl, etc.); C_{7-19} aralkyl (e.g., benzyl, diphenylmethyl, etc.) which may be substituted with C_{1-3} alkylenedioxy (e.g., methylenedioxy, etc.); C_{8-19} arylalkenyl (e.g., 3-phenyl-2-prop-2-enyl, etc.); 5- to 8-monocyclic non-aromatic heterocyclic group-C_{1-6} alkyl (e.g., pyrrolidinylmethyl etc.); C_{6-14} aryl-amino-C_{1-6} alkyl (e.g., 2,6-dimethylphenylaminomethyl, etc.) which may be substituted with 1 to 3 C_{1-6} alkyl; etc. More preferably, Rb is C_{6-14} aryl which may be substituted.

[0154] Z is preferably CH.

[0155] In the formula (I""), as the "hydrocarbon group which may be substituted" represented by Rc, those exemplified as the above Rb can be mentioned. Preferably, Rc is C_{6-14} aryl which may be substituted.

[0156] As the "nitrogen-containing heterocyclic ring which may be substituted" formed by R^2 together with the adja-

cent nitrogen atom and Y, those exemplified as the "nitrogen-containing heterocyclic ring which may be substituted" formed by R^1 and R^2 together with the adjacent nitrogen atom can be mentioned.

[0157] Suitable examples of the compounds represented by the formula (I) include those represented by the formulas (I'), (I"), (I'''), (I''''), (I'''''), etc.

[0158] Among the compounds represented by the formula (I), those represented by the formulas (I'), (I"), (I'''') or (I'''') are novel compounds.

[0159] Suitable examples of the compounds represented by the formula (I') include the following compounds:

(E)-3-[1-[4-[(4-methoxybenzyl)oxy]benzoyl]-2,3-dihydro-1H-indol-5-yl]-N,N-dimethyl-2-propene-l-amine;
(E)-3-[1-[4-[(4-methylbenzyl)oxy]benzoyl]-2,3-dihydro-1H-indol-5-yl]-N,N-dimethyl-2-propene-1-amine;
(E)-3-[1-[4-[(4-chlorobenzyl)oxy]benzoyl]-2,3-dihydro-1H-indol-5-yl]-N,N-dimethyl-2-propene-1-amine;
1-[[6-(4-chlorophenyl)-3-pyridinyl]carbonyl]-6-[(E)-3-(1-pyrrolidinyl)-1-propenyl]-1,2,3,4-tetrahydroquinoline;

1-[[6-(4-fluorophenyl)-3-pyridinyl]carbonyl]-6-[(E)-3-(1-pyrrolidinyl)-1-propenyl]-1,2,3,4-tetrahydroquinoline;
1-[[6-(4-methylphenyl)-3-pyridinyl]carbonyl]-6-[(E)-3-(1-pyrrolidinyl)-1-propenyl]-1,2,3,4-tetrahydroquinoline;
1-[[6-(4-chlorophenyl)-3-pyridinyl]carbonyl]-6-[(E)-3-dimethylamino-l-propenyl]-1,2,3,4-tetrahydroquinoline;
1-[[6-(4-fluorophenyl)-3-pyridinyl]carbonyl]-6-[(E)-3-dimethylamino-1-propenyl]-1,2,3,4-tetrahydroquinoline;
1-[[6-(4-methylphenyl)-3-pyridinyl]carbonyl]-6-[(E)-3-dimethylamino-1-propenyl]-1,2,3,4-tetrahydroquinoline;
1-[[6-(4-chlorophenyl)-3-pyridinyl]carbonyl]-6-[(E)-4-(1-pyrrolidinyl)-1-butenyl]-1,2,3,4-tetrahydroquinoline;
1-[[6-(4-fluorophenyl)-3-pyridinyl]carbonyl]-6-[(E)-4-(1-pyrrolidinyl)-1-butenyl]-1,2,3,4-tetrahydroquinoline;
1-[[6-(4-methylphenyl)-3-pyridinyl]carbonyl]-6-[(E)-4-(1-pyrrolidinyl)-1-butenyl]-1,2,3,4-tetrahydroquinoline;
1-[[6-(4-chlorophenyl)-3-pyridinyl)carbonyl]-6-[(E)-4-dimethylamino-1-butenyl]-1,2,3,4-tetrahydroquinoline;
1-[[6-(4-fluorophenyl)-3-pyridinyl]carbonyl]-6-[(E)-4-dimethylamino-1-butenyl]-1,2,3,4-tetrahydroquinoline;
1-[[6-(4-methylphenyl)-3-pyridinyl]carbonyl]-6-[(E)-4-dimethylamino-1-butenyl]-1,2,3,4-tetrahydroquinoline;
(E)-N,N-dimethyl-3-[1-[[4-(4-methylphenyl)-1-piperidinyl]carbonyl]-1,2,3,4-tetrhydro-6-quinolinyl]-2-propen-1-amine;
(E)-N,N-dimethyl-3-[1-[[4-(4-fluorophenyl)-1-piperidinyl]carbonyl]-1,2,3,4-tetrhydro-6-quinolinyl]-2-propen-1-amine;
(E)-N,N-dimethyl-3-[1-[[4-(4-chlorophenyl)-1-piperidinyl]carbonyl]-1,2,3,4-tetrhydro-6-quinolinyl]-2-propen-1-amine;
1-[[4-(4-methylphenyl)-1-piperidinyl]carbonyl]-6-[(E)-3-(1-pyrrolidinyl)-1-propenyl]-1,2,3,4-tetrahydroquinoline;
1-[[4-(4-fluorophenyl)-1-piperidinyl]carbonyl]-6-[(E)-3-(1-pyrrolidinyl)-1-propenyl]-1,2,3,4-tetrahydroquinoline;
1-[[4-(4-chlorophenyl)-1-piperidinyl]carbonyl]-6-[(E)-3-(1-pyrrolidinyl)-1-propenyl]-1,2,3,4-tetrahydroquinoline;
(E)-3-[1-[[4-(4-chlorophenyl)-1-piperazinyl]carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-N,N-dimethyl-2-propen-1-amine;
(E)-3-[1-[[4-(4-methylphenyl)-1-piperazinyl]carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-N,N-dimethyl-2-propen-1-amine;
(E)-3-[1-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-N,N-dimethyl-2-propen-1-amine;
1-[[5-(4-fluorophenyl)-2-pyridinyl]carbonyl]-6-[(E)-3-(1-pyrrolidinyl)-1-propenyl]-1,2,3,4-tetrahydroquinoline;
1-[[5-(4-methylphenyl)-2-pyridinyl]carbonyl]-6-[(E)-3-(1-pyrrolidinyl)-1-propenyl]-1,2,3,4-tetrahydroquinoline;
1-[[6-(4-chlorophenyl)-3-pyridinyl]carbonyl]-6-[1-methyl-3-piperidinylidene)methyl-1,2,3,4-tetrahydroquinoline;
1-[[5-(4-chlorophenyl)-2-furoyl]-6-[(E)-3-(4-phenyl-1-piperidinyl)-1-propenyl]-1,2,3,4-tetrahydroquinoline.

[0160] Suitable examples of the compounds represented by the formula (I") include the following compounds:

4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(1,2,3,4-tetrahydro-7-isoquinolinyl)-1-butanone;
4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone;
4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(3-methyl 2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone;
4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(3-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-1-butanone;
4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(3-propyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone;
1-(3-benzyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-butanone;
1-(3-acetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-butanone;
4-[4-(4-chlorophenyl)piperidin-1-yl]-1-(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxobutan-1-one;
4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)-1-butanone;
4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(2-methyl-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)-4-oxo-1-butanone;
4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(2,3-dihydro-1H-isoindol-5-yl)-4-oxo-1-butanone.

[0161] In addition to the above compounds represented by the formula (I') or (I"), suitable examples of the compound represented by the formula (I) include the following compounds:

(E)-3-[1-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-N,N-dimethyl-2-propen-1-amine;
1-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-6-[(E)-3-piperidino-1-propenyl]-1,2,3,4-tetrahydroquinoline;
(E)-3-[1-[([1,1'-biphenyl]-4-yl)carbonyl]-2,3-dihydro-1H-indol-5-yl]-N,N-dimethyl-2-propen-1-amine;
(E)-3-[1-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-2,3-dihydro-1H-indol-5-yl]-N,N-dimethyl-2-propen-1-amine;
(E)-4-[1-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-N,N-dimethyl-3-buten-1-amine;
1-(3-acetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-1-butanone;
4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone;
4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone;
4-oxo-N-(2-phenethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide;
4-oxo-N-(3-phenylpropyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide;
N-[2-(1H-indol-3-yl)ethyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide.

[0162] Further, suitable examples of the compounds represented by the formula (I) include the following compounds:

7-[3-[4-(4-chlorophenyl)piperidin-1-yl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-3-cyclopentyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-benzyl-7-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-acetyl-7-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-3-isobutyryl-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-benzoyl-7-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
tert-butyl 7-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-1,2,4,5-tetrahydro-1H-3-benzazepine-3-carboxylate;
7-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-3-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-N-ethyl-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxamide;
7-[3-[4-(4-fluorophenyl)-1-piperidinyl]propoxy]-3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-[3-[4-(2,4-difluorophenyl)-1-piperidinyl]propoxy]-3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-[3-[4-(4-methylphenyl)-1-piperidinyl]propoxy]-3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-isopropyl-7-[3-[4-(3-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-isopropyl-7-[3-[4-(2-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-isopropyl-7-[3-[4-(4-methoxyphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-isopropyl-7-[3-[4-(3-trifluoromethylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-acetyl-7-[3-[4-(4-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-acetyl-7-[3-[4-(4-methoxyphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-isobutyryl-7-[3-[4-(4-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-isobutyryl-7-[3-[4-(4-methoxyphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-[3-[4-(4-methylphenyl)-1-piperidinyl]propoxy]-3-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-3-benzazepine;
7-[3-[4-(4-methoxyphenyl)-1-piperidinyl]propoxy]-3-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-acetyl-7-[3-[4-(4-fluorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-acetyl-7-[3-[4-(3-fluorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-acetyl-7-[3-[4-(2,4-difluorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-acetyl-7-[3-[4-(4-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-acetyl-7-[3-[4-(3-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-acetyl-7-[3-[4-(2-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-acetyl-7-[3-[4-(4-methoxyphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-3-benzazepine;
3-[(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]-N-[3-(4-methylphenyl)propyl]propanamide;
N-[3-(4-chlorophenyl)propyl]-3-[(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]propanamide;
N-[3-(3-chlorophenyl)propyl]-3-[(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]propanamide;
N-[3-(2-chlorophenyl]propyl]-3-[(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]propanamide;
3-(4-chlorophenyl)-N-[3-[(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)oxy]propyl]-1-propanamine;
(E)-4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-2-buten-1-one;
(E)-4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-2-buten-1-one;
(E)-4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-2-buten-1-one;

8-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-3-isopropyl-2,3,4,5-tetrahydro-1H-2-benzazepine;
8-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-3-cyclopentyl-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-benzyl-8-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
8-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-2-isobutyryl-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-benzoyl-8-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
8-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-2-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-2-benzazepine;
8-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-N-ethyl-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxamide;
8-[3-[4-(4-fluorophenyl)-1-piperidinyl]propoxy]-2-isopropyl-2,3,4,5-tetrahydro-1H-2-benzazepine;
8-[3-[4-(2,4-difluorophenyl)-1-piperidinyl]propoxy]-2-isopropyl-2,3,4,5-tetrahydro-1H-2-benzazepine;
8-[3-[4-(4-methylphenyl)-1-piperidinyl]propoxy]-2-isopropyl-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-isopropyl-8-[3-[4-(3-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-isopropyl-8-[3-[4-(2-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-isopropyl-8-[3-[4-(4-methoxyphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-isopropyl-8-[3-[4-(3-trifluoromethylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-acetyl-8-[3-[4-(4-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-acetyl-8-[3-[4-(4-methoxyphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-isobutyryl-8-[3-[4-(4-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-isobutyryl-8-[3-[4-(4-methoxyphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
8-[3-[4-(4-methylphenyl)-1-piperidinyl]propoxy]-2-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-2-benzazepine;
8-[3-[4-(4-methoxyphenyl)-1-piperidinyl]propoxy]-2-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-acetyl-8-[3-[4-(4-fluorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-acetyl-8-[3-[4-(3-fluorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-acetyl-8-[3-[4-(2,4-difluorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-acetyl-8-[3-[4-(4-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-acetyl-8-[3-[4-(3-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-acetyl-8-[3-[4-(2-methylphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
2-acetyl-8-[3-[4-(4-methoxyphenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine;
3-[(2-isopropyl-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)oxy]-N-[3-(4-methylphenyl)propyl]propanamide;
N-[3-(4-chlorophenyl)propyl]-3-[(2-isopropyl-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)oxy]propanamide;
N-[3-(3-chlorophenyl)propyl]-3-[(2-isopropyl-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)oxy]propanamide;
N-[3-(2-chlorophenyl)propyl]-3-[(2-isopropyl-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)oxy]propanamide;
3-(4-chlorophenyl)-N-[3-[(2-isopropyl-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)oxy]-1-propanamine.

[0163] Examples of salts of compound (I), (I'), (I"), (I'"), (I'"") or (I'""") include salts with inorganic bases, ammonium salts, salts with organic bases, salts with inorganic acids, salts with organic acids, salts with basic or acidic amino acids, and the like.

[0164] Preferred examples of salts with inorganic bases include alkali metal salts such as sodium salts, potassium salts, etc.; alkaline earth metal salts such as calcium salts, magnesium salts, barium salts, etc.; aluminum salts; etc.

[0165] Preferred examples of salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc.

[0166] Preferred examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

[0167] Preferred examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

[0168] Preferred examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc. Preferred examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

[0169] Among these salts, pharmaceutically acceptable salts are preferred. For example, when compound (I), (I'), (I"), (I'"), (I'"") or (I'""") possesses an acidic functional group, it can form an inorganic salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, barium salt, etc.), etc., an ammonium salt, etc. When compound (I), (I'), (I"), (I'"), (I'"") or (I'""") possesses a basic functional group, it can form an inorganic salt such as hydrochloride, sulfate, phosphate, hydrobromate, etc.; or an organic salt such as acetate, maleate, fumarate, succinate, methanesulfonate, p-toluenesulfonate, citrate, tartrate, etc.

[0170] Compounds (I), (I'), (I"), (I'"), (I'"") and (I'""") (hereinafter also abbreviated as the compound of the present invention) can be either anhydrides or hydrates. A hydrate may have 0.5 to 3 water molecules.

[0171] In addition, the compounds of the invention can be labeled using isotopes (e.g. ^{3}H, ^{14}C, and ^{35}S, etc.).

[0172] When the compound of the present invention contain optical isomers, stereoisomers, regio isomers, rotational isomers, these are also included as the compound of the present invention, and each of them can be obtained as a

single substance by per se known synthesis methods and separation methods. For example, when optical isomers exist in the compound of the present invention, the optical isomers resolved from the compound are included in the compound of the present invention.

[0173] The optical isomers can be produced using per se known methods. Specifically, the optical isomer can be obtained by using an optically active synthetic intermediate, or subjecting a racemic mixture of the final product to optical resolution in accordance with common method.

[0174] Examples of optical resolution methods include per se known methods such as the fractional recrystallization method, chiral column method, diastereomer method, etc., which are described in detail below.

1) Fractional recrystallization method

[0175] The method which comprises allowing a racemate to form a salt with an optically active compound (e.g. (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.), separating the salt using a fractional recrystallization method, followed by, if desired, neutralizing process to obtain a free optical isomer.

2) Chiral column method

[0176] This method comprises subjecting a racemate or its salt to a column for separating an optical isomer (chiral column) for separation. For example, in the case of liquid chromatography, an optical isomer mixture is added to the chiral column such as ENANTIO-OVM [produced by Toso] or CHIRAL series [produced by Daicel], which is developed using water, various buffer solutions (e.g. phosphate buffer), organic solvents (e.g. ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, etc.) as single or mixed solutions, and the optical isomers are separated. Also, in the case of gas chromatography, for example, separation is conducted using a chiral column such as CP-Chiras-il-DeX CB (produced by G.L.Science Co.).

3) Diastereomer method

[0177] In this method, a racemic mixture is subjected to a chemical reaction with an optically active reagent to give a diastereomer mixture, which is separated into a single substance by an ordinary separation means (e.g. fractional recrystallization, chromatography method, etc.). This single substance is subjecting to removal of the optically active reagent part using chemical processing such as a hydrolysis reaction. For example, when a compound of the invention possesses hydroxy or primary or secondary amino in its molecule, this compound is subjected to a condensation reaction with an optically active organic acid (e.g. MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid], (-)-menthoxyacetic acid, etc.), to give the diastereomer in an ester form or an amide form, respectively. On the other hand, when a compound of the invention possesses carboxylic acid group, this compound is subjected to a condensation reaction with an optically active amine or alcohol reagent, to give the diastereomer in an amide form or an ester form, respectively. The separated diastereomer can be converted to an optical isomer of the original compound, by applying acidic hydrolysis or basic hydrolysis.

[0178] A prodrug of compound (I') or (I") is a compound which is converted to compound (I') or (I") by reactions involving enzymes and gastric acid, etc. under physiological conditions in the living body; in other words, a compound that is changed into compound (I') or (I") by enzymatically-caused oxidation, reduction and hydrolysis, and a compound that is changed into compound (I') or (I") by hydrolysis caused by gastric acid. Examples of the prodrugs of compound (I') or (I") include compounds in which amino groups of compound (I') or (I") have been acylated, alkylated, or phosphorylated [e.g. compounds in which amino groups of compound (I') or (I") have been eicosanoylated, aranylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated, etc.]; compounds in which hydroxyl groups of compound (I') or (I") have been acylated, alkylated, phosphorylated, borated (e.g. compounds in which hydroxyl groups of compound (I') or (I") have been acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarilated, alanilated, dimethylaminomethylcarbonylated, etc.); compounds in which carboxyl groups of compound (I') or (I") have been esterified or amidated [e.g. compounds in which carboxyl groups of compound (I') or (I") have been ethylesterified, phenylesterified, carboxylmethylesterified, dimethylaminomethylesterified, pivaloyloxymethylesterified, ethoxycarbonyloxyethylesterified, phthalidylesterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylesterified, cyclohexyloxycarbonylethylesterified, or methylamidated, etc.]. These compounds can be produced from compound (I') or (I") using per se known methods.

[0179] Also, a prodrug of compound (I') or (I") can be a compound which is changed to compound (I') or (I") by physiological conditions, as described in pages 163 to 198 of Molecular Design, Volume 7, "Development of Drugs", published in 1990 by Hirokawa Shoten.

[0180] Prodrugs of compounds (I), (I'''), (I''''') and (I''''') may also be used. As prodrugs of these compounds, those exemplified as prodrugs of the above compound (I') or (I") can be mentioned.

[0181] The compound of the present invention can be produced by [Production method 1] to [Production method 10] which are described in detail below, or analogous methods thereto.

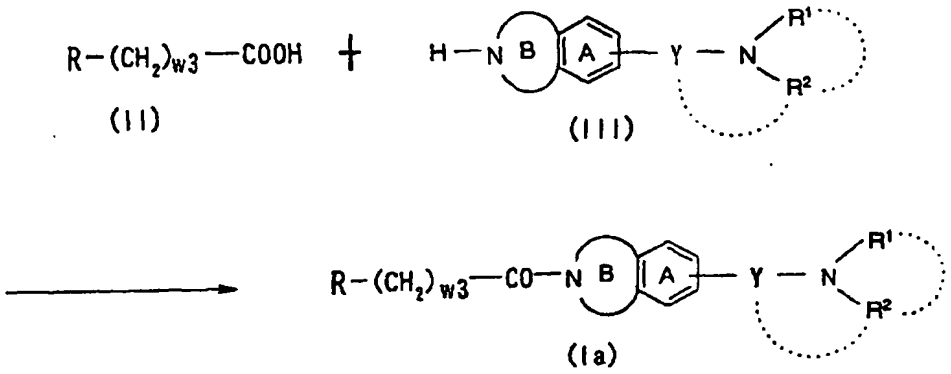
[0182] Compound (II), compound (III), compound (V), compound (VI), compound (IIa), compound (IIb), compound (IIIa), compound (IIIaa), compound (IIIab), compound (IIIac), compound (IIIb), compound (IIIc), compound (IVa), compound (IVb), compound (IVc), compound (IVd), compound (Va), compound (VIa), compound (VIaa), compound (VIIa), compound (VIId), compound (VIIg), compound (VIIIe), compound (IXa), compound (IXb), compound (IXe), compound (IXg), compound (Xa), compound (Xb), compound (Xf), compound (XIa), compound (XIf) and compound (XIg) used as raw materials can be used in the form of salts, respectively. As such salts, those exemplified as salts of the above compound (I), etc. can be used.

[0183] In the following [Production method 1] to [Production method 10], when an alkylation reaction, a hydrolysis reaction, an amination reaction, an esterification reaction, an amidation reaction, an esterification reaction, an etherification reaction, an oxidation reaction, a reducing reaction, etc. are carried out, these reactions are carried out in accordance with per se known methods. Examples of such methods include the methods described in Organic Functional Group Preparations, Second Edition, Academic Press, Inc., published in 1989; Comprehensive Organic Transformations, VCH Publishers Inc., published in 1989, etc.

[Production method 1]

[0184] Compound (Ia) having $-(CH_2)_{w3}CO-$ (w3 is as defined above) for X in the formula (I) is produced, for example, by the following amidation reaction.

(Amidation reaction)



wherein the symbols are as defined above.

[0185] The "amidation reaction" includes the following "method using a dehydration and condensation agent" and "method using a reactive derivative of carboxylic acid".

i) Method using a dehydration and condensation agent

[0186] Compound (III), 1 to 5 equivalents of compound (II), and 1 to 2 equivalents of a dehydration and condensation agent are reacted in an inert solvent. If necessary, the reaction can be carried out with the coexistence of 1 to 1.5 equivalents of 1-hydroxybenzotriazole (HOBT) and/or catalytic quantity to 5 equivalents of a base.

[0187] Examples of the "dehydrating and condensation agent" include dicyclohexylcarbodimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodimide hydrochloride (WSC). WSC is particularly preferable.

[0188] Examples of the "inert solvent" include nitrile solvents (preferably acetonitrile), amide solvents (preferably DMF), halogenated hydrocarbon solvents (preferably dichloromethane), ether solvents (preferably THF). Two or more kinds of these can be mixed in an appropriate ratio for use.

[0189] Examples of the "base" include

1) for example, strong bases such as hydrides of alkali metals or alkaline earth metals (e.g. lithium hydride, sodium hydride, potassium hydride, calcium hydride, etc.), amides of alkali metals or alkaline earth metals (e.g. lithium amide, sodium amide, lithium diisopropylamide, lithium dicyclohexylamide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, etc.), lower alkoxides of alkali metals or alkaline earth metals (e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.), etc.;
2) for example, inorganic bases such as hydroxides of alkali metals or alkaline earth metals (e.g. sodium hydroxide, potassium hydroxide, lithium hydroxide, barium hydroxide, etc.), carbonates of alkali metals or alkaline earth metals (e.g. sodium carbonate, potassium carbonate, cesium carbonate, etc.) and hydrogencarbonates of alkali metals or alkaline earth metals (e.g. sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), etc.; and
3) for example, organic bases exemplified by amines such as triethylamine, diisopropylethylamine, N-methylmorpholine, dimethylaminopyridine, DBU (1,8-diazabicyclo[5.4.0]undec-7-en), DBN (1,5-diazabicyclo[4.3.0]non-5-en), etc.; basic heterocyclic compounds such as pyridine, imidazole, 2,6-lutidine, etc.; and the like.

[0190] Among the above bases, triethylamine, 4-dimethylaminopyridine, etc., are preferable.

[0191] Reaction temperature is usually room temperature (0°C to 30°C, hereafter the same). Reaction time is, for example, 10 to 24 hours.

ii) Method using a reactive derivative of carboxylic acid

[0192] A reactive derivative of compound (II) and 1 to 5 equivalents (preferably 1 to 3 equivalents) of compound (III) are reacted in an inert solvent. If necessary, the reaction can be carried out with the coexistence of 1 to 10 equivalents, preferably 1 to 3 equivalents of a base.
Examples of the "reactive derivative" of compound (II) include acid halides (e.g., acid chloride, acid bromide, etc.), mixed acid anhydrides (e.g. acid anhydrides with C_{1-6} alkyl-carboxylic acid, C_{6-10} aryl-carboxylic acid or C_{1-6} alkylcarbonate), active esters (e.g. esters with phenol which may be substituted, 1-hydroxybenzotriazole or N-hydroxysuccinimide, etc.), etc.

[0193] Examples of the "substituents" in the "phenol which may be substituted" include halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), nitro, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkoxy. The number of substituents is, for example, 1 to 5.

[0194] As the "optionally halogenated C_{1-6} alkyl" and "optionally halogenated C_{1-6} alkoxy", those exemplified as "substituents" in the above "cyclic group which may be substituted" can be used.

[0195] Specific examples of "phenol which may be substituted" include phenol, pentachlorophenol, pentafluorophenol, p-nitrophenol, etc. The reactive derivative is, preferably, an acid halide.

[0196] Examples of the "inert solvent" include ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents, and water. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, THF, dichloromethane, chloroform, etc. are preferable.

[0197] As the "base", the same as above are used. The base is preferably sodium hydride, potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, pyridine, etc.

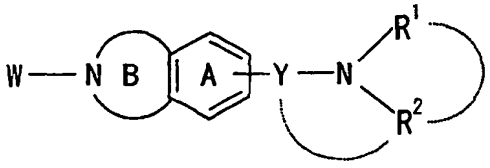
[0198] Reaction temperature is usually -20°C to 50°C, preferably room temperature. Reaction time is usually 5 minutes to 40 hours, preferably 1 to 18 hours.

[0199] Further, the compound of the formula (I) wherein X is $-(CH_2)_{w3}SO_2-$ or $-(CH_2)_{w3}SO-$ (the symbols are as defined above) can be produced by subjecting a sulfonic acid of the formula $R-(CH_2)_{w3}-SO_2OH$ (the symbols are as defined above) or a sulfinic acid of the formula $R-(CH_2)_{w3}-SOOH$ (the symbols are as defined above) to the same method as the above "method using a reactive derivative of carboxylic acid".

[0200] Compound (II) can be produced by per se known methods or analogous methods thereto.

[0201] Compound (III) can be produced by per se known methods, for example, the methods described in Chem. Pharm. Bull., 36, 4377(1988), JP 9-506885 A, JP 10-504315 A, etc. or analogous methods thereto.

[0202] For example, compound (III) can be produced by subjecting the compound of the formula:



(IIIa)

wherein W is a protecting group for amino; and the other symbols are as defined above, to a deprotection reaction to remove W.

[0203] Examples of the protecting group for amino represented by W include formyl, C_{1-6} alkyl-carbonyl (e.g. acetyl, propionyl, etc.), C_{1-6} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.), benzoyl, C_{7-10} aralkyl-carbonyl (e.g. benzylcarbonyl, etc.), C_{7-14} aralkyloxy-carbonyl (e.g. benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, etc.), trityl, phthaloyl, N,N-dimethylaminomethylene, silyl (e.g. trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl, etc.), C_{2-6} alkenyl (e.g. 1-allyl, etc.), etc. These groups may be substituted by 1 to 3 of halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, etc.) or nitro, etc.

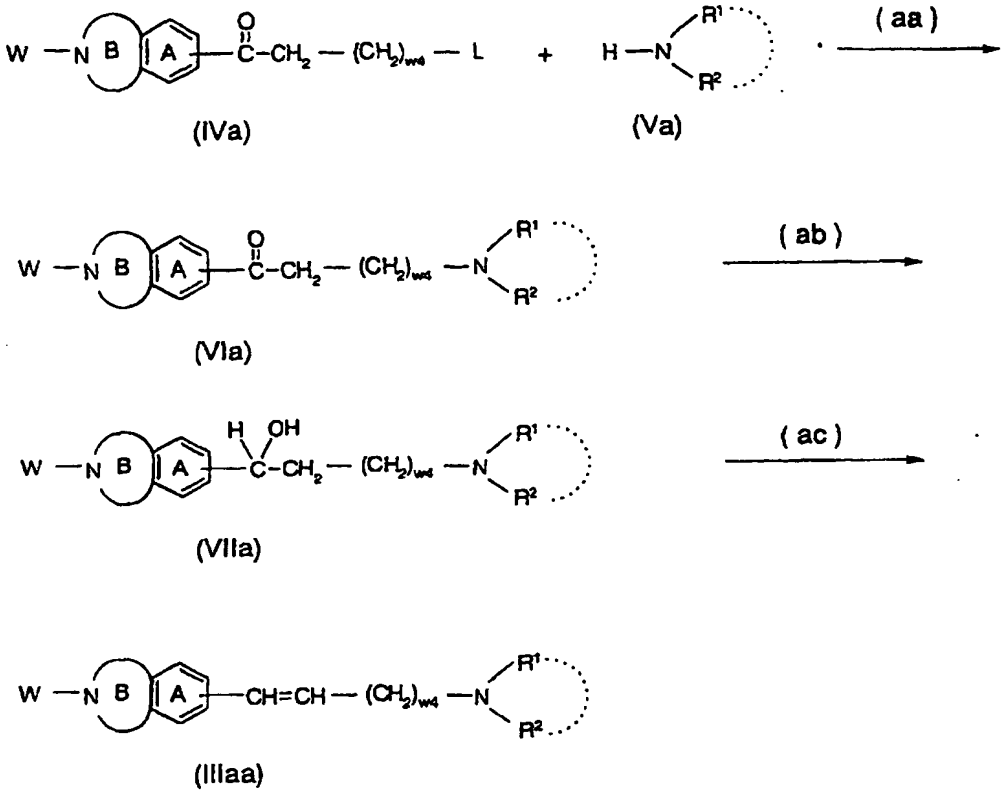
[0204] The deprotection reaction is carried out, for example, by maintaining compound (IIIa), preferably at 20°C to 140°C, in an aqueous solution of an acid such as a mineral acid (e.g., hydrochloric acid, sulfuric acid, hydrobromic acid, iodic acid, periodic acid, etc.) etc., or a base such as an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, lithium hydroxide, etc.) etc. The acid or base is usually used in an amount of 1 to 100 equivalents, preferably 1 to 40 equivalents based on compound (IIIa). Strength of the acid or base is usually 0.1 N to 18 N, preferably 1 N to 12 N. Reaction time is usually 0.5 hour to 48 hours, preferably 1 hour to 24 hours.

[0205] Further, when W is t-butoxycarbonyl group, etc., the deprotection reaction can also be carried out by dissolving compound (IIIa) in an organic acid (e.g., trifluoroacetic acid, formic acid, acetic acid, methanesulfonic acid, benzenesulfonic acid, trifluoromethanesulfonic acid, etc.) and maintaining the solution usually at -20°C to 200°C, preferably 0°C to 100°C. The organic acid is used in an amount of 1 to 100 equivalents, preferably 1 to 40 equivalents based on compound (IIIa).

[0206] The deprotection reaction can also be carried out by subjecting compound (IIIa) to catalytic reduction in an alcoholic solvent, for example, ethanol, etc., or a solvent such as acetic acid, etc., with a catalyst such as palladium, palladium-carbon, Raney nickel, Raney cobalt, platinum oxide, etc. at normal pressure or, if necessary, under pressure.

[0207] Compound (IIIa) can be produced by per se known methods or analogous methods thereto. For example, compound (IIIa) wherein Y is C_{2-6} alkenylene [e.g., $-CH=CH-(CH_2)_{w4}-$ (w4 is as defined above)], i.e., compound (IIIaa), can be produced, for example, according to the following [Reaction scheme 1-1].

[Reaction scheme 1-1]



wherein L is a leaving group and the other symbols are as defined above.

[0208] In the step (aa), compound (VIa) is produced by a condensation reaction of compound (IVa) and compound (Va).

[0209] Examples of the "leaving group" represented by L include halogen atom (e.g. chlorine, bromine, iodine, etc.), optionally halogenated C_{1-6} alkylsulfonyloxy (e.g. methanesulfonyloxy, ethanesulfonyloxy, trifluoromethanesulfonyloxy, etc.), C_{6-10} arylsulfonyloxy which may be substituted, hydroxy, etc.

[0210] Examples of the "substituents" in the "C_{6-10} arylsulfonyloxy which may be substituted" include halogen atom (e.g. chlorine, bromine, iodine, etc.), optionally halogenated C_{1-6} alkyl, C_{1-6} alkoxy, etc. The number of substituents is, for example, 1 to 3. Specific examples of the C_{6-10} arylsulfonyloxy which may be substituted" include benzenesulfonyloxy, p-toluenesulfonyloxy, 1-naphthalenesulfonyloxy, 2-naphthalenesulfonyloxy, etc.

[0211] The "leaving group" is preferably halogen atom (e.g. chlorine, bromine, iodine, etc.), methanesulfonyloxy, trifluoromethanesulfonyloxy, p-toluenesulfonyloxy, etc.

[0212] This reaction is usually carried out in an inert solvent.

[0213] Examples of the "inert solvent" include alcohol solvents, ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents, water, etc. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, N,N-dimethylformamide (DMF), acetone, ethanol, pyridine, etc., are preferred.

[0214] Compound (Va) is used in an amount of 1 equivalent to 100 equivalents based on compound (IVa). Further, compound (Va) can be used in an amount corresponding to a reaction solvent.

[0215] Reaction temperature is about -20°C to 200°C, preferably room temperature to 100°C. Reaction time is, for example, 0.5 hour to 1 day.

[0216] This condensation reaction may be carried out in the presence of a base. The base is preferably sodium

hydride, potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, pyridine, etc. The amount of the base is 0.1 to 100 equivalents, preferably 1 to 10 equivalents based on compound (IVa).

[0217] Compound (IVa) can be produced by a per se known method or an analogous method thereto. For example, compound (IVa) can be produced by the method described in JP 6-166676 A, etc. or an analogous method thereto.

[0218] Further, compound (Va) can be produced by a per se known method or an analogous method thereto.

[0219] In the step (ab), compound (VIIa) is produced by subjecting compound (VIa) to a reducing reaction.

[0220] This reducing reaction can be carried out by using a reducing agent such as sodium borohydride, lithium aluminum hydride, triethylsilane, etc.

[0221] The reducing reaction can be carried out, for example, according to the methods described in Reduction with Complex Metal Hydrides, Interscience, New York (1956); Chem. Soc. Rev., 5, 23 (1976); Synthesis, 633 (1974); J. Am. Chem. Soc., 91, 2967 (1969); J. Org. Chem., 29, 121 (1964); Org. Reactions, 1, 15 (1942); Angew. Chem., 71, 726 (1956); Synthesis, 633 (1974); J. Am. Chem. Soc., 80, 2896 (1958); Org. Reactions, 4, 378 (1948); J. Am. Chem. Soc., 108, 3385 (1986); etc., or analogous methods thereto.

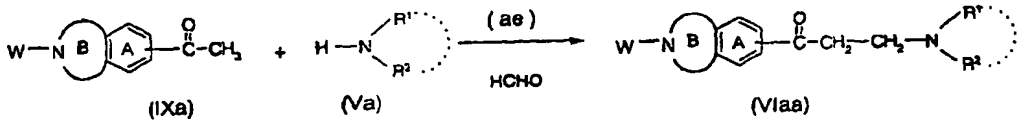
[0222] In the step (ac), compound (IIIaa) is produced by subjecting compound (VIIa) to dehydration reaction.

[0223] This dehydration reaction can be carried out with heating or at room temperature, if necessary, by using an acid catalyst (e.g., sulfuric acid, phosphoric acid, potassium hydrogen sulfate, p-toluenesulfonic acid, boron trifluoride-ether complex, iodine, etc.). Further, the dehydration reaction can also be carried out by using an activating agent such as thionyl chloride-pyridine, phosphorus oxychloride-pyridine, etc.

[0224] The dehydration reaction can be carried out, for example, according to the methods described in Org. Synth., I, 183 (1941); Org. Synth., I, 430 (1941); Org. Synth., III, 204 (1955); Org. Synth., VI, 307 (1988); Synthesis, III, 1159 (1980); J. Am. Chem. Soc., 106, 6690 (1984); Tetrahedron Lett., 599 (1871); etc., or analogous methods thereto.

[0225] Further, compound (VIa) used in [Reaction scheme 1-1] wherein w4 is 1, i.e., compound (VIaa), can be produced, for example, by subjecting compound (IXa), compound (Va) and formaldehyde to Mannich reaction according to the following [Reaction scheme 1-2].

[Reaction scheme 1-2]



(IXa) (Va) (VIaa)

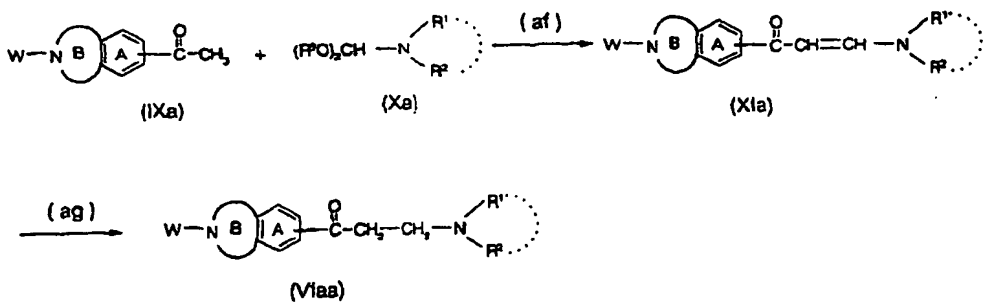
wherein the symbols are as defined above.

[0226] Mannich reaction in the step (ae) can be carried out, for example, according to the methods described in Org. Reactions, 1, 303 (1942); Tetrahedron Lett., 18, 1299 (1977); etc., or analogous methods thereto.

[0227] Compound (IXa) can be produced by a per se known method or an analogous method thereto. For example, compound (IXa) can be produced according to the method described in J. Chem. Soc., Perkin Trans. 1, 2993 (1994), etc., or an analogous method thereto.

[0228] Compound (VIaa) can also be produced by the following

[Reaction scheme 1-3].



wherein R^9 is C_{1-6} alkyl and the other symbols are as defined above.

[0229] As the "C_{1-6} alkyl" represented by R^9, the same as the "C_{1-6} alkyl" represented by the above R^4 can be mentioned.

[0230] That is, compound (VIaa) can be produced by carrying out in turn the step (af): the condensation reaction of compound (IXa) and (Xa); and the step (ag): the reducing reaction of compound (XIa).

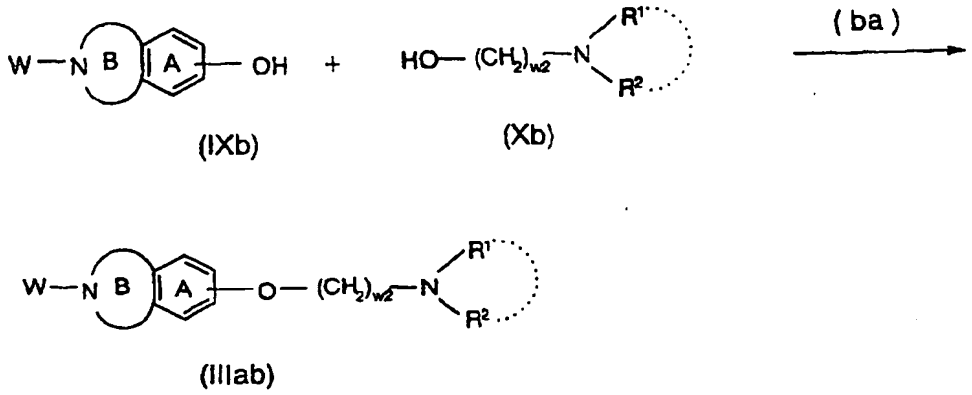
[0231] The step (af) can be carried out by using a per se known condensation reaction. The condensation reaction can be carried out, for example, by the methods described in J. Heterocyclic Chem., 30, 23 (1993); Heterocycles, 22, 195 (1984); etc., or analogous methods thereto.

[0232] Compound (Xa) can be produced by a per se known method or an analogous method thereto.

[0233] The step (ag) can be carried out by using a per se known reducing reaction (e.g., catalytic reduction using a transition metal catalyst such as Pd/C, etc.; reducing reaction using a metal hydride such as Et_3SiH, etc.; reducing reaction using a metal hydrogen complex such as $NaBH(OAc)_3$, etc.). For example, the reducing reaction can be carried out by the methods described in J. Am. Chem. Soc., 76, 5014 (1954); Bull. Chem. Soc. Jpn., 45, 3506 (1972); etc., or analogous methods thereto.

[0234] Compound (IIIa) wherein Y is $-O-(CH_2)_{w2}-$ (w2 is as defined above), i.e., compound (IIIab), can be produced by subjecting compound (IXb) and compound (Xb) to a dehydration reaction, for example, under the conditions of Mitsunobu reaction according to the following [Reaction scheme 2-1].

[Reaction scheme 2-1]



wherein the symbols are as defined above.

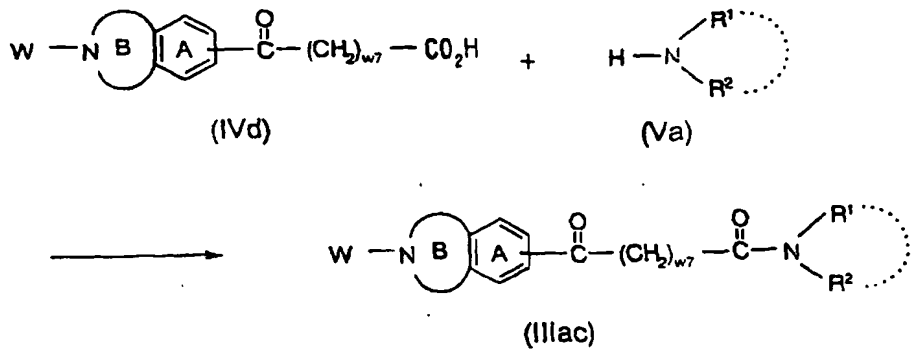
[0235] The dehydration reaction in the step (ba) can be carried out, for example, according to the methods described in Synthesis, 1 (1981); Bull. Chem. Soc. Jpn., 49, 510 (1976); etc., or analogous methods thereto.

[0236] Compound (IXb) can be produced by a per se known method or an analogous method thereto.

[0237] Compound (Xb) can be produced by a per se known method or an analogous method thereto.

[0238] Compound (IIIa) wherein Y is -CO-$(CH_2)_{w7}$-CO- (w7 is as defined above), i.e., compound (IIIac) can be synthesized by subjecting compound (IVd) and compound (Va) to the above "amidation reaction" according to the following [Reaction scheme 2-2].

[Reaction scheme 2-2]



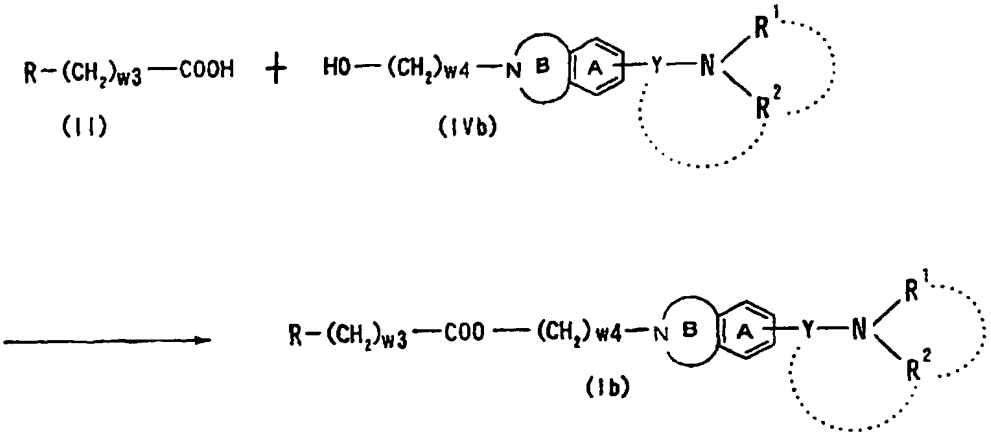
wherein the symbols are as defined above.

[0239] Compound (IVd) can be produced according to a per se known method or an analogous method thereto.

[Production method 2]

[0240] Compound (I) wherein X is - $(CH_2)_{w3}$-COO$(CH_2)_{w4}$- (the symbols are as defined above), i.e., compound (Ib), can be produced by the following esterification reaction.

(Esterification reaction)



wherein the symbols are as defined above.

[0241] In this reaction, a reactive derivative of compound (II) and 1 to 5 equivalents (preferably 1 to 3 equivalents) of compound (IVb) is reacted in an inert solvent, usually, in the presence of 1 to 10 equivalents, preferably 1 to 3

equivalents of a base.

[0242] As the reactive derivative of compound (II), that exemplified in the above [Production method 1] is used. Especially, an acid halide is preferable.

[0243] Examples of the "inert solvent" include ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, dichloromethane, chloroform, etc. are preferable.

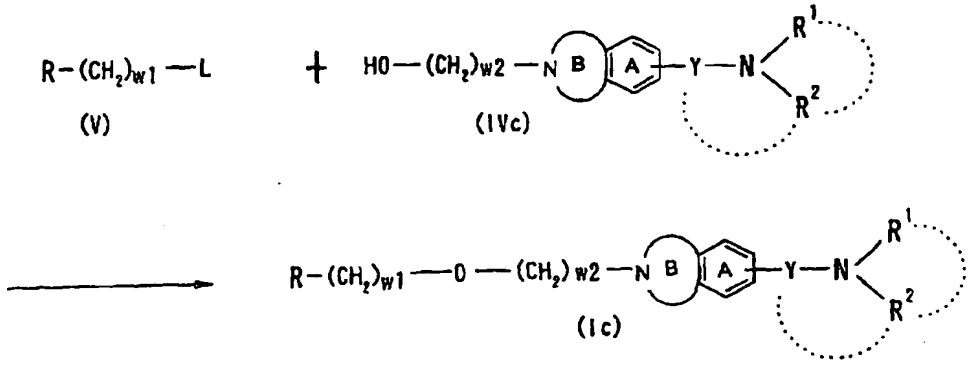
[0244] As the "base", that exemplified in the above [Production method 1] can be used. The base is preferably sodium hydride, potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, pyridine, etc.

[0245] Reaction temperature is usually -20°C to 50°C, preferably room temperature. Reaction time is usually 5 minutes to 40 hours, preferably 1 to 18 hours.

[Production method 3]

[0246] Compound (I) wherein X is-$(CH_2)_{w1}O(CH_2)_{w2}$- (the symbols are as defined above), i.e., compound (Ic), can be produced by, for example, the following etherification reaction.

(Etherification reaction)



wherein the symbols are as defined above.

[0247] In this reaction, compound (IVc) and about 1 to 5 equivalents (preferably 1 to 2 equivalents) of compound (V) are reacted in inert solvent in the presence of base.

[0248] As the "base", that exemplified in the above [Production method 1] can be used. The base is preferably potassium carbonate, sodium hydrogencarbonate, triethylamine, N-methylmorpholine, pyridine, etc.

[0249] The amount of the base used is usually about 1 to 5 equivalents based on compound (V).

[0250] Examples of the "inert solvent" include alcohol solvents, ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents, water. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, N,N-dimethylformamide (DMF), acetone, ethanol, pyridine, etc., are preferable.

[0251] Reaction temperature is about -20°C to 100°C, preferably room temperature to 80°C. Reaction time is, for example, about 0.5 hour to 1 day.

[0252] When the leaving group for L in compound (V) is hydroxy, compound (Ic) can be produced by using Mitsunobu reaction.

[0253] The Mitsunobu reaction is carried out by reacting compound (V) and 0.5 to 5 equivalents (preferably 1 to 1.5 equivalents) of compound (IVc) in inert solvent in the coexistence of 0.5 to 5 equivalents (preferably 1 to 1.5 equivalents) of ethyl acetyldicarboxylate.

[0254] Examples of the inert solvent include ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, dichloromethane, chloroform, etc. are preferable.

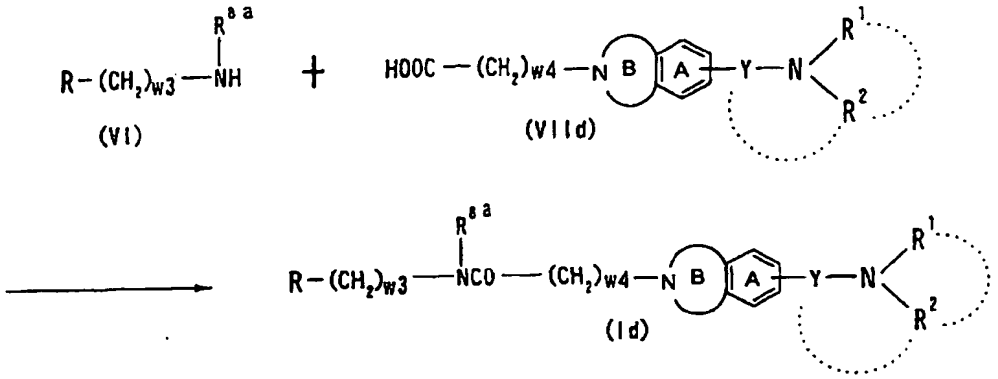
[0255] Reaction temperature is usually -20°C to 50°C, preferably room temperature. Reaction time is usually 5 minutes to 40 hours, preferably 1 to 18 hours.

[0256] Compound (IVc) can be produced by a per se known method.

[Production method 4]

[0257] Compound (I) wherein X is $-(CH_2)_{w3}NR^{8a}CO(CH_2)_{w4}-$ (the symbols are as defined above), i.e., compound (Id), can be produced, for example, by the following amidation reaction.

(Amidation reaction)



wherein R^{8a} is hydrogen atom or optionally halogenated C_{1-6} alkyl and the other symbols are as defined above.

[0258] As the "optionally halogenated C_{1-6} alkyl" represented by R^{8a}, that exemplified with respect to the above R^8 can be mentioned.

[0259] This reaction is carried out in accordance with the above [Production method 1].

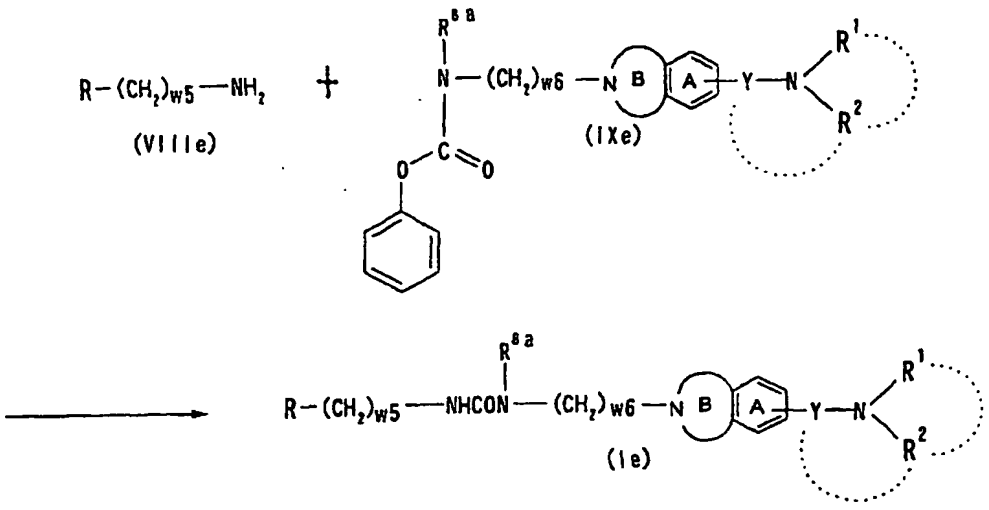
[0260] Compound (VI) can be produced by a per se known method.

[0261] Compound (VIId) can be produced by a per se known method.

[Production method 5]

[0262] Compound (I) wherein X is $-(CH_2)_{w5}NHCONR^{8a}(CH_2)_{w6}-$ (the symbols are as defined above), i.e., compound (Ie), can be produced, for example, by the following urea reaction.

(Urea reaction)



wherein the symbols are as defined above.

[0263] In this reaction, compound (IXe) and 1 to 5 equivalents (preferably 1 to 1.5 equivalents) of compound (VIIIe) is reacted in an inert solvent in the coexistence of a base.

[0264] As the "base", that exemplified in the above {Production method 1] can be used. The base is preferably potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine, pyridine, etc.

[0265] Examples of the "inert solvent" include alcohol solvents, ether solvents, halogenated hydrocarbon solvents, aromatic solvents, nitrile solvents, amide solvents, ketone solvents, sulfoxide solvents, water. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, acetonitrile, DMF, acetone, ethanol, pyridine, etc. are preferable.

[0266] Reaction temperature is usually -20°C to 100°C, preferably room temperature to 80°C. Reaction time is, for example, 0.5 hour to 1 day.

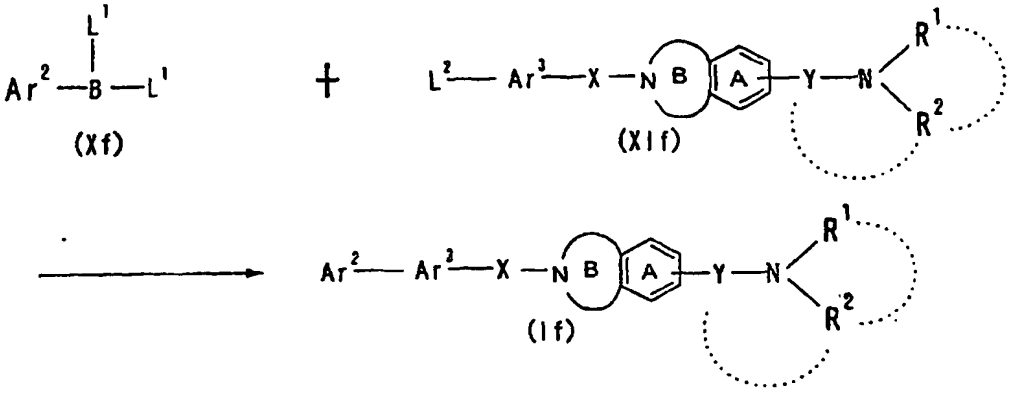
[0267] Compound (VIIIe) can be produced by a per se known method.

[0268] Compound (IXe) can be produced by a per se known method.

[Production method 6]

[0269] Compound (I) wherein R is a ring assembly aromatic group (Ar^2-Ar^3) which may be substituted, i.e., compound (If), can be produced by, for example, the following aryl-coupling reaction.

(Aryl-coupling reaction)



wherein Ar^2 and Ar^3 are monocyclic aromatic groups or condensed aromatic groups, each of which may be substituted; L^1 is hydroxy or C_{1-6} alkyl; L^2 is halogen (preferably chlorine, bromine) or trifluoromethanesulfonyloxy; the other symbols are as defined above.

[0270] As "substituents", "monocyclic aromatic groups" and "condensed aromatic groups" in the "monocyclic aromatic groups or condensed aromatic groups, each of which may be substituted" represented by Ar^2 and Ar^3, those exemplified as the above R and Ar^1 can be used. Especially, it is preferable that both of Ar^2 and Ar^3 are phenyl groups which may be substituted, and Ar^2-Ar^3 is biphenylyl which may be substituted.

[0271] The aryl-coupling reaction can be carried out in accordance with per se known methods such as the method described in Acta. Chemica Scandinavia, pp. 221-230, 1993, or methods analogous thereto.

[0272] In this reaction, compound (Xf) and 1 to 3 equivalents (preferably 1 to 1.5 equivalents) of compound (XIf) are reacted in an inert solvent in the presence of a base and a transition metal catalyst.

[0273] As the base, that exemplified in the above [Production method 1] can be used. The base is preferably sodium carbonate, sodium hydrogencarbonate, etc.

[0274] The amount of the "base" used is, for example, about 1 to 10 equivalents based on compound (XIf).

[0275] Examples of the "transition metal catalyst" include palladium catalyst, nickel catalyst. Examples of the "palladium catalyst" include tetrakis(triphenylphosphine)palladium (O), palladium acetate, bis (triphenylphosphine) palladium (II) chloride, palladium-carbon, etc. Examples of the "nickel catalyst" include tetrakis(triphenylphcsphine) nickel (O), etc.

[0276] The amount of the "transition metal catalyst" used is about 0.01 to 1 equivalent, preferably about 0.01 to 0.5 equivalent, based on compounc (XIf).

[0277] Reaction temperature is room temperature to 150°C, preferably about 80°C to 150°C. Reaction time is, for example, about 1 to 48 hours.

[0278] Examples of the "inert solvent" include water, alcohol solvents, aromatic solvents. Two or more kinds of these can be mixed in an appropriate ratio for use. Especially, a single solvent such as water, ethanol and toluene; or a mixed solvent of two or more kinds of these is preferred.

[0279] Compound (Xf) can be produced by a per se known method.

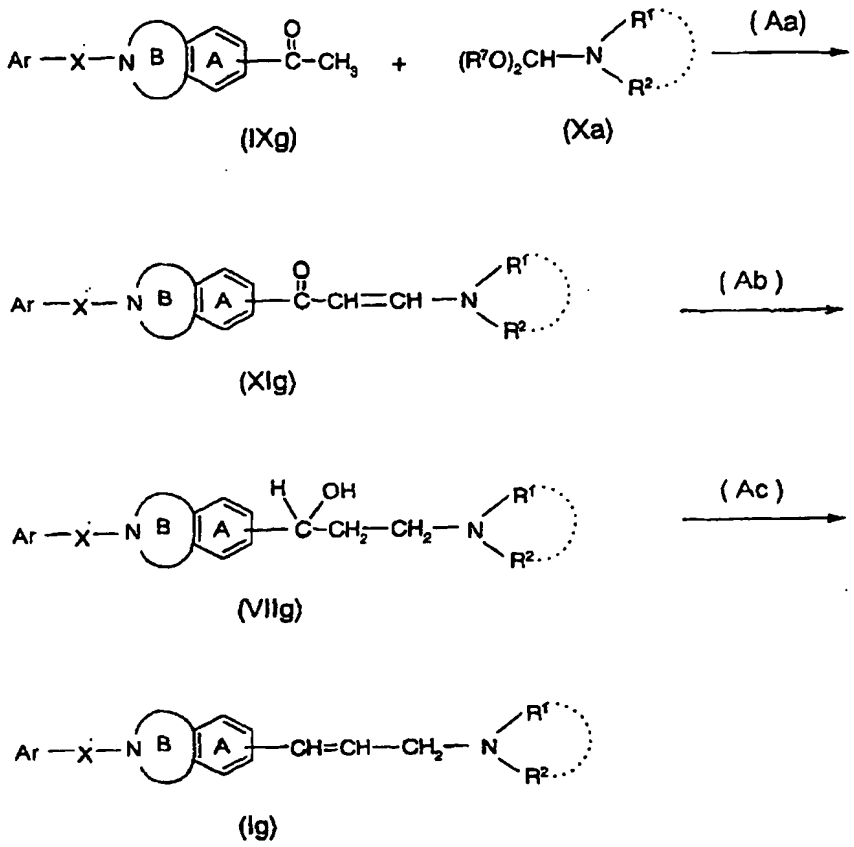
[0280] Compound (XIf) can be produced by a per se known method.

[Production method 7]

[0281] Compound (I) wherein Y is C_{2-6} alkenylene (e.g., $CH=CHCH_2$), i.e., compound (Ig) can be produced by the following [Reaction scheme 3-1].

[0282] That is, compound (Ig) can be produced by carrying out in turn the step (Aa): a condensation reaction of compound (IXg) and compound (Xa); the step (Ab): a reducing reaction of compound (XIg); and the step (Ac): a dehydration reaction of compound (VIIg).

[Reaction scheme 3-1]



wherein the symbols are as defined above.

[0283] The condensation reaction of the step (Aa) can be carried out, for example, according to the same manner as that in the above step (af).

[0284] The reducing reaction of the step (Ab) can be carried out, for example, by a per se known method (e.g., catalytic reduction using a transition metal catalyst such as Pd/C, etc.; reducing reaction using a metal hydride such as Et_3SiH, etc.; reducing reaction using a metal hydrogen complex such as $NaBH_4$, etc.).

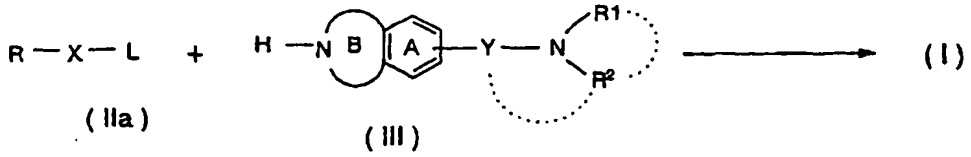
[0285] Further, this reaction can be carried out by a two-stage reaction, for example, by reducing the double bond under the same conditions as those of the above reducing reaction of the step (ag), followed by reducing the carbonyl group with a metal hydrogen complex such as $NaBH_4$, etc.

[0286] The dehydration reaction of the step (Ac) can be carried out by the same manner as that in the above step (ac).

[0287] Compound (IXg) can be produced by a per se known method.

[0288] Compound (I) can also be produced by subjecting compound (IIa) and compound (III) to a condensation reaction according to the following [Production method 8]. The "condensation reaction" can be carried out according to the same manner as the condensation reaction in the above step (aa).

[Production method 8]

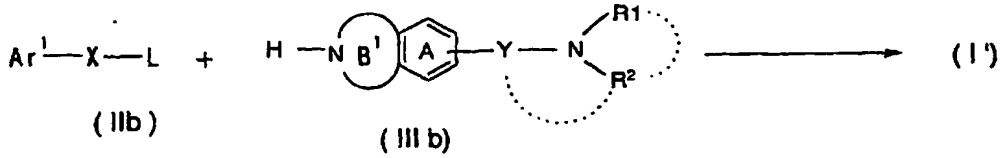


wherein the symbols are as defined above.

[0289] Compound (IIa) can be produced by a per se known method or an analogous method thereto.

[0290] Compound (I') can be produced by subjecting compound (IIb) and compound (IIIb) to a condensation reaction, for example, according to the following [Production method 9]. The "condensation reaction" can be carried out according to the same manner as the condensation reaction in the above step (aa).

[Production method 9]



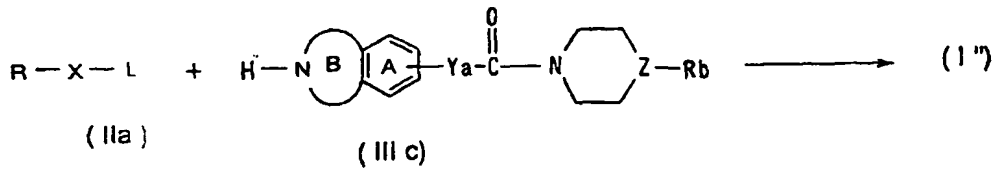
wherein the symbols are as defined above.

[0291] Compound (IIb) can be produced by a per se known method or an analogous method thereto.

[0292] Compound (IIIb) can be produced according to the same manner as that for the above compound (III).

[0293] Compound (I") can be produced by subjecting compound (IIa) and compound (IIIc) to a condensation reaction according to, for example, the following [Production method 10]. The "condensation reaction" can be carried out according to the same manner as the condensation reaction in the above step (aa).

[Production method 10]



wherein the symbols are as defined above.

[0294] Compound (IIIc) can be produced according to the same manner as the above compound (III).

[0295] Examples of the above "alcohol solvents" include methanol, ethanol, isopropanol, tert-butanol, etc.

[0296] Examples of the above "ether solvents" include diethylether, tetrahydrofuran (THF), 1,4-dioxane, 1,2-dimethoxyethane, etc.

[0297] Examples of the above "halogenated hydrocarbon solvents" include dichloromethane, chloroform, 1,2-dichloroethane, carbon tetrachloride, etc.

[0298] Examples of the above "aromatic solvents" include benzene, toluene, xylene, pyridine, etc.

[0299] Examples of the above "hydrocarbon solvents" include hexane, pentane, cyclohexane, etc.

[0300] Examples of the above "amide solvents" include N,N-dimethylformamide (DMF), N,N-dimethylacetamide, N-

methylpyrrolidone, etc.

[0301] Examples of the above "ketone solvent" include acetone, methylethylketone, etc.

[0302] Examples of the above "sulfoxide solvents" include dimethylsulfoxide (DMSO), etc.

[0303] Examples of the above "nitrile solvents" include acetonitrile, propionitrile, etc.

[0304] In a compound of the invention thus obtained, the intramolecular functional group can be converted to a desired functional group by combining per se known chemical reactions. Examples of the chemical reactions include oxidation reaction, reducing reaction, alkylation reaction, hydrolysis reaction, amination reaction, esterification reaction, aryl-coupling reaction, deprotection reaction.

[0305] In each of the above reactions, when the starting material compounds possess amino, carboxy, hydroxy, and/or carbonyl as substituents, protecting groups which are generally used in peptide chemicals, etc., can be introduced into these groups, and the desired compound can be obtained by removing the protecting groups after the reaction if necessary.

[0306] Examples of the protecting group for amino include those exemplified with respect to the above W.

[0307] Examples of the protecting group for carboxy include C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), C_{7-11} aralkyl (e.g. benzyl, etc.), phenyl, trityl, silyl (e.g. trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl, etc.), C_{2-6} alkenyl (e.g. 1-allyl, etc.). These groups may be substituted by 1 to 3 of halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, etc.) or nitro.

[0308] Examples of the protective group for hydroxy include C_{1-6} alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, trityl, C_{7-10} aralkyl (e.g. benzyl, etc.), formyl, C_{1-6} alkyl-carbonyl (e.g. acetyl, propionyl, etc.), benzoyl, C_{7-10} aralkyl-carbonyl (e.g. benzylcarbonyl, etc.), 2-tetrahydropyranyl, 2-tetrahydrofuranyl, silyl (e.g. trimethylsilyl, triethylsilyl, dimethylphenylsilyl, tert-butyldimethylsilyl, tert-butyldiethylsilyl, etc.), C_{2-6} alkenyl (e.g. 1-allyl, etc.). These groups may be substituted by 1 to 3 of halogen atom (e.g. fluorine, chlorine, bromine, iodine, etc.), C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl, etc.), C_{1-6} alkoxy (e.g. methoxy, ethoxy, propoxy, etc.) or nitro, etc.

[0309] Examples of the protecting group for carbonyl include cyclic acetal (e.g. 1,3-dioxane, etc.), and non-cyclic acetal (e.g. di-C_{1-6} alkylacetal, etc.).

[0310] Removal of the above protecting groups can be carried out in accordance with per se known methods such as those described in Protective Groups in Organic Synthesis, published by John Wiley and Sons (1980). For instance, the methods using acid, base, ultraviolet light, hydrazine, pheny1Hydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate, trialkylsilyl halide (e.g. trimethylsilyl iodide, trimethylsilyl bromide, etc.), and a reduction method, etc. can be used.

[0311] The compound of the present invention can be isolated and purified by per se known methods such as solvent extraction, changing of liquid properties, transdissolution, crystallization, recrystallization, chromatography, etc. It is also possible to isolate and purify the starting material compounds of the compound of the present invention, or their salts using the same known methods as above, but they can also be used as raw materials in the next process as a reaction mixture without being isolated.

[0312] The compound of the present invention possesses an excellent MCH receptor antagonistic action, therefore, it is useful as an agent for preventing or treating diseases caused by MCH. Also, the compound of the present invention is low in toxicity, and is excellent in oral absorbency and intracerebral transitivity.

[0313] Therefore, a melanin-concentrating hormone antagonist comprising a compound of the invention can be safely administered to mammals (e.g. rats, mice, guinea pigs, rabbits, sheep, horses, swine, cattle, monkeys, humans, etc.) as an agent for preventing or treating diseases caused by MCH.

[0314] Here, examples of the diseases caused by MCH include obesity (e.g. malignant mastocytosis, exogenous obesity, hyperinsulinar obesity, hyperplasmic obesity, hypophyseal adiposity, hypoplasmic obesity, hypothyroid obesity, hypothalamic obesity, symptomatic obesity, infantile obesity, upper body obesity, alimentary obesity, hypogonadal obesity, systemic mastocytosis, simple obesity, central obesity, etc.], hyperphagia, emotional disorders, reproductive function disorders, etc.

[0315] The compound of the present invention is also useful as an agent for preventing or treating lifestyle diseases such as diabetes, diabetic complications (e.g. diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, etc.), arteriosclerosis, gonitis, etc.

[0316] Further, the compound of the present invention is useful as an anorectic agent.

[0317] The MCH antagonist and the pharmaceutical composition of the present invention can be used in combination with an alimentary therapy (e.g., alimentary therapy for diabetes) and exercise.

[0318] The MCH antagonist and the pharmaceutical composition of the present invention can be produced by subjecting the compound of the present invention, as it is, or together with a pharmacologically acceptable carrier, to pharmaceutical manufacturing process in accordance with a per se known means.

[0319] Here, examples of the pharmacologically acceptable carriers include various organic or inorganic carrier substances which are commonly used as materials for pharmaceutical preparations, such as excipients, lubricants, binders,

and disintegrators in solid preparations; solvents, solubilizing agents, suspending agents, isotonizing agents, buffering agents, soothing agents, in liquid preparations; and the like. Also, in the pharmaceutical manufacturing process, additives such as antiseptics, antioxidants, coloring agents, sweeteners, absorbents, moistening agents, etc., can be used, if necessary.

[0320] Examples of the excipients include lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light anhydrous silicic acid, etc.

[0321] Examples of the lubricants include magnesium stearate, calcium stearate, talc, colloidal silica, etc.

[0322] Examples of the binders include crystalline cellulose, sucrose, D-mannitcl, dextrin, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, starch, saccharose, gelatin, methylcellulose, carboxymethylcellulose sodium, etc.

[0323] Examples of the disintegrators include starch, carboxymethylcellulose, carboxymethylcellulose calcium, crosscarmellose sodium, carboxymethylstarch sodium, low-substituted hydroxypropylcellulose (L-HPC), etc.

[0324] Examples of the solvents include distilled water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, etc.

[0325] Examples of the solubilizing agents include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc.

[0326] Examples of the suspending agents include surfactants such as stearyltriethanolamine, sodium lauryl sulfate, lauryl amino propionic acid, lecithin, benzalkonium chloride, benzethonium chloride, glyceryl monostearate; or hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose sodium, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, etc.

[0327] Examples of the isotonizing agents include glucose, D-sorbitol, sodium chloride, glycerin, D-mannitol, etc.

[0328] Examples of the buffering agents include buffer solutions of phosphate, acetate, carbonate, citrate, etc.

[0329] Examples of the soothing agents include benzyl alcohol, etc.

[0330] Examples of the antiseptics include paraoxybenzoates, chlorobutanol, benzyl alcohol, phenethylalcohol, dehydroacetic acid, sorbic acid, etc.

[0331] Examples of the antioxidants include sulfite, ascorbic acid, etc.

[0332] The MCH antagonist and the pharmaceutical composition of the present invention can be safely administered orally or parenterally (e.g. by local, rectal and intravenous administration) in various dosage forms, for example, as oral drugs such as tablets (including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), solutions; and parenteral preparations such as injectable preparations (e.g. preparations for subcutaneous injections, intravenous injections, intramuscular injections, intraperitoneal injections, etc.), external preparations (e.g. nasal preparations, percutaneous preparations, ointments, etc.), suppositories (e.g. rectal suppositories, vaginal suppositories, etc.), sustained-release preparations (e.g. sustained-release microcapsules, etc.), pellets, drip infusions, etc.

[0333] The content of the compound of the present invention in the MCH antagonist of the present invention and the content of the compound of the present invention in the pharmaceutical composition of the present invention are, for example, about 0.1 to 100% by weight based on the total weight of the MCH antagonist or pharmaceutical composition, respectively.

[0334] The dose of the MCH antagonist and the pharmaceutical composition of the present invention can be appropriately selected depending on the subject of administration, route of administration, disease, etc.

[0335] For example, the dose per day when the MCH antagonist or the pharmaceutical composition of the present invention is orally administered to an adult obesity patient (body weight: about 60 kg), is about 0.1 to about 500 mg, preferably about 1 to about 100 mg, more preferably about 5 to about 100 mg, in terms of the compound of the present invention which is an active ingredient. This amount can be divided into one to several doses per day for administration.

[0336] The MCH antagonist and pharmaceutical composition of the present invention can be used in combination with other concomitant drugs which do not interfere with the MCH antagonist and pharmaceutical composition of the present invention, for the purpose of "strengthening of therapeutic effect against obesity", "reduction of dose of MCH antagonist", etc. Examples of the concomitant drugs include a "agents for treating diabetes", "agents for treating diabetic complications", "agents for treating obesity other than MCH antagonists", "agents for treating hypertension", "agents for treating hyperlipidemia", "agents for treating arthritis", "antianxiety agents", "antidepressant", etc. Two or more kinds of these concomitant drugs can be combined in an appropriate ratio for use.

[0337] Examples of the above "agents for treating diabetes" include insulin sensitizers, insulin secretion enhancers, biguanides, insulins, α-glucosidase inhibitors, β3 adrenaline receptor agonists, etc.

[0338] Examples of the insulin sensitizers include pioglitazone or its salt (preferably hydrochloride), troglitazone, rosiglitazone or its salt (preferably maleate), JTT-501, GI-262570, MCC-555, YM-440, DRF-2593, BM-13-1258, KRP-297, R-119702, etc.

[0339] Examples of the insulin secretion enhancers include sulfonylureas. Specific examples of the sulfonylureas include tolbutamide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide and its ammonium salt, clibencla-

mide, gliclazide, glimepiride, etc.

[0340] Other than the above, examples of insulin secretion enhancers include repaglinide, nateglinide, mitiglinide (KAD-1229), JTT-608, etc.

[0341] Examples of biguanides include metformin, buformin, phenformin, etc.

[0342] Examples of insulins include animal insulins extracted from bovine or porcine pancreas; semi-synthetic human insulin which is enzymatically synthesized from insulin extracted from porcine pancreas; human insulin synthesized by genetic engineering, using Escherichia coli and yeast; etc. As insulin, also employed are insulin-zinc containing 0.45 to 0.9 (w/w)% of zinc; protamine-insulin-zinc produced from zinc chloride, protamine sulfate and insulin; etc. In addition, insulin can be an insulin fragment or derivative (e.g. INS-1, etc.).

[0343] Insulin can also include various types such as ultra immediate action type, immediate action type, two-phase type, intermediate type, prolonged action type, etc., and these can be selected depending on the pathological conditions of patients.

[0344] Examples of α-glucosidase inhibitors include acarbose, voglibose, miglitol, emiglitate, etc.

[0345] Examples of β3 adrenaline receptor agonists include AJ-9677, BMS-196085, SB-226552, AZ40140, etc.

[0346] Other than the above, examples of the "agents for treating diabetes" include ergoset, pramlintide, leptin, BAY-27-9955, etc.

[0347] Examples of the above "agents for treating diabetic complications" include aldose reductase inhibitors, glycation inhibitors, protein kinase C inhibitors, etc.

[0348] Examples of aldose reductase inhibitors include torlestat; eparlestat; imirestat; zenarestat; SNK-860; zopolrestat; ARI-509; AS-3201, etc.

[0349] Examples of glycation inhibitors include pimagedine.

[0350] Examples of protein kinase C inhibitors include NGF, LY-333531, etc.

[0351] Other than the above, examples of "agents for treating diabetic complications" include alprostadil, thiapride hydrochloride, cilostazol, mexiletine hydrochloride, ethyl eicosapentate, memantine, pimagedline (ALT-711), etc.

[0352] Examples of the above "agents for treating obesity other than MCH antagonists" include lipase inhibitors and anorectics, etc.

[0353] Examples of lipase inhibitors include orlistat, etc.

[0354] Examples of anorectics include mazindol, dexfenfluramine, fluoxetine, sibutramine, baiamine, etc.

[0355] Other than the above, examples of "agents for treating obesity other than MCH antagonists" include lipstatin, etc.

[0356] Examples of the above "agents for treating hypertension" include angiotensin converting enzyme inhibitors, calcium antagonists, potassium channel openers, angiotensin II antagonists, etc.

[0357] Examples of angiotensin converting enzyme inhibitors include captopril, enarapril, alacepril, delapril (hydrochloride), lisinopril, imidapril, benazepril, cilazapril, temocapril, trandolapril, manidipine (hydrochloride), etc.

[0358] Examples of calcium antagonists include nifedipine, amlodipine, efonidipine, nicardipine, etc.

[0359] Examples of potassium channel openers include levcromakalim, L-27152, AL0671, NIP-121, etc.

[0360] Examples of angiotensin II antagonists include losartan, candesartan cilexetil, valsartan, irbesartan, CS-866, E4177, etc.

[0361] Examples of the above "agents for treating hyperlipidemia (agents for treating arteriosclerosis)" include HMG-CoA reductase inhibitors, fibrate compounds, etc.

[0362] Examples of HMG-CoA reductase inhibitors include pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, lipantil, cerivastatin, itavastatin, ZD-4522, or their salts (e.g. sodium salts, etc.), etc.

[0363] Examples of fibrate compounds include bezafibrate, clinofibrate, clofibrate, simfibrate, etc.

[0364] Examples of the above "agents for treating arthritis" include ibuprofen, etc.

[0365] Examples of the above "antianxiety agents" include chlordiazepoxide, diazepam, oxazolam, medazepam, cloxazolam, bromazepam, lorazepam, alprazolam, fludiazepam, etc.

[0366] Examples of the above "antidepressants" include fluoxetine, fluvoxamine, imipramine, paroxetine, sertraline, etc.

[0367] The timing of administration of the above concomitant drugs is not limited. The MCH antagonist or pharmaceutical composition and the concomitant drugs can be administrated to the subject simultaneously or at staggered times.

[0368] The dosages of the concomitant drugs can be determined in accordance with clinically used dosages, and can be appropriately selected according to the subject of administration, route of administration, diseases and combinations of drugs, etc.

[0369] The administration forms for the concomitant drugs are not particularly limited as long as the MCH antagonist or the pharmaceutical composition are used in combination with a concomitant drugs at the time of administration. Examples of such administration forms includes 1) administration of a single preparation obtained by simultaneous preparation of MCH antagonist or pharmaceutical composition together with concomitant drugs, 2) simultaneous ad-

ministration of two kinds of preparations obtained by separate preparation of MCH antagonist or pharmaceutical composition, and concomitant drugs, through the same route of administration, 3) staggered administration of two kinds of preparations obtained by separate preparation of MCH antagonist or pharmaceutical composition, and concomitant drugs, through the same route of administration, 4) simultaneous administration of two kinds of preparations obtained by separate preparation of MCH antagonist or pharmaceutical composition, and concomitant drugs, through different routes of administration, 5) staggered administration of two kinds of preparations obtained by separate preparation of MCH antagonist or pharmaceutical composition, and concomitant drugs, through different routes of administration (for example, administration of MCH antagonist or pharmaceutical composition; and concomitant drugs in this order; or administration in reverse order).

[0370] The ratio of combination of MCH antagonist or pharmaceutical composition with concomitant drugs can be appropriately selected in accordance with the subject of administration, route of administration and diseases, etc.

BEST MODE FOR CARRYING OUT THE INVENTION

[0371] The present invention will be explained further in detail by the following Reference Examples, Examples, Preparation Examples, and Experimental Examples. However, these do not limit the present invention, and they can be changed within the scope that does not deviate from the scope of the present invention.

[0372] In the following Reference Examples and Examples, "room temperature" means 0 to 30°C. Anhydrous magnesium sulfate or anhydrous sodium sulfate was used to dry the organic layer. "%" means percent by weight, unless otherwise specified.

[0373] Infrared absorption spectra were determined by the diffuse reflectance method, using fourier transform type infrared spectrophotometer.

[0374] FABMS (pos) is mass spectrum determined by the (+) method, in Fast Atom Bombardment Mass Spectrometry.

[0375] MS (APCI) and MS (ESI) are mass spectra determined by Atmospheric Pressure Chemical Inonization (APCI) or Electron Spray Ionization (ESI), respectively.

[0376] Other symbols used in the description have the following meanings.

s :	singlet
d :	doublet
t :	triplet
q :	quartet
m :	multiplet
br :	broad
J :	coupling constant
Hz :	Hertz
$CDCl_3$:	heavy chloroform
DMSO-d_6 :	heavy dimethylsulfoxide
THF :	tetrahydrofuran
DMF :	N,N-dimethylformamide
DMSO :	dimethylsulfoxide
WSCD :	1-ethyl-3-(3-dimethylaminopropyl) carbodimide
WSC :	1-ethyl-3-(3-dimethylaminopropyl) carbodimide hydrochloride
^{1}H-NMR :	: proton nuclear resonance
	(Free substances were usually measured in $CDCl_3$.)
IR :	infrared absorption spectrum
Me :	methyl
Et :	ethyl
HOBt :	1-hydroxy-1H-benzotriazole
IPE :	diisopropyl ether
DMAP :	4-dimethylaminopyridine

[0377] In this specification and drawings, when bases and amino acids are shown by codes, these codes are based on those by the IUPAC-IUB Commission on Biochemical Nomenclature or common codes in the concerned fields. Examples of these codes are shown below. Also, where some optical isomers of amino acids can exist, the L form is shown unless otherwise specified.

DNA : deoxyribonucleic acid

cDNA :	complementary deoxyribonucleic acid
A :	adenine
T :	thymine
G :	guanine
C :	cytosine
RNA :	ribonucleic acid
mRNA :	messenger ribonucleic acid
dATP :	deoxyadenosine triphosphate
dTTP :	deoxythymidine triphosphate
dGTP :	deoxyguanosine triphosphate
dCTP :	deoxycytidine triphosphate
ATP :	adenosine triphosphate
EDTA :	ethylenediamine tetraacetic acid
SDS :	sodium dodecyl sulfate
EIA :	enzyme immunoassay
Gly :	glycine
Ala :	alanine
Val :	valine
Leu :	leucine
Ile :	isoleucine
Ser :	serine
Thr :	threonine
Cys :	cysteine
Met :	methionine
Glu :	glutamic acid
Asp :	aspartic acid
Lys :	lysine
Arg :	arginine
His :	histidine
Phe :	phenylalanine
Tyr :	tyrosine
Tro :	tryptophan
Pro :	proline
Asn :	asparagine
Gln :	glutamine
pGl :	pyroglutamine
Me :	methyl group
Et :	ethyl group
Bu :	butyl group
Ph :	phenyl group
TC :	thiazolidine-4(R)-carboxamide group

[0378] Substituents, protecting groups and reagents frequently used in this specification, are shown by the following symbols.

Tos :	p-toluenesulfonyl
CHO :	formyl
Bzl :	benzyl
Cl_2Bzl :	2,6-dichlorobenzyl
Bom :	benzyloxymethyl
Z :	benxyloxycarbonyl
Cl-Z :	2-chlorobenzyloxycarbonyl
Br-Z :	2-bromobenzyloxycarbonyl
Boc :	t-butoxycarbonyl
DNP :	dinitrophenol
Trt :	trityl
Bum :	t-butoxymethyl
Fmoc :	N-9-fluorenylmethoxycarbonyl

HOOBt : 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine
HONB : 1-hydroxy-5-norbornene-2,3-dicarbodiimide
DCC : N,N'-dicyclohexylcarbodiimide

SEQ ID NO in the SEQUENCE LISTING in the specification of the present application shows the following sequences.
[SEQ ID NO: 1] shows a synthetic DNA used for screening of cDNA coding rat SLC-1.
[SEQ ID NO: 2] shows a synthetic DNA used for screening of cDNA coding rat SLC-1.
[SEQ ID NO: 3] shows an entire amino acid sequence of rat SLC-1.
[SEQ ID NO: 4] shows an entire base sequence of rat SLC-1cDNA wherein Sal I recognition sequence was added to the 5' side, and Spe I recognition sequence was added to the 3' side.
[SEQ ID NO: 5] shows riboprobe used to determine the quantity of SLC-1mRNA expressed in each clone of rat SLC-1 expression CHO cells.
[SEQ ID NO: 6] shows a synthetic DNA used to obtain cDNA for coding of human SLC-1.
[SEQ ID NO: 7] shows a primer used to make double-strand cDNA for coding human SLC-1.
[SEQ ID NO: 8] shows an entire base sequence of cDNA for coding human SLC-1.
[SEQ ID NO: 9] shows an entire amino acid sequence of human SLC-1.
[SEQ ID NO: 10] shows a synthetic DNA used for screening of cDNA for coding human SLC-1(S).
[SEQ ID NO: 11] shows a synthetic DNA used for screening of cDNA for coding human SLC-1(S).
[SEQ ID NO: 12] shows a synthetic DNA used for screening of cDNA for coding human SLC-1(L).
[SEQ ID NO: 13] shows a synthetic DNA used for screening of cDNA for coding human SLC-1(L).
[SEQ ID NO: 14] shows an entire base sequence of human SLC-1(S) cDNA wherein Sal I recognition sequence was added to the 5' side, and Spe I recognition sequence was added to the 3' side.
[SEQ ID NO: 15] shows an entire base sequence of human SLC-1(L) cDNA wherein Sal I recognition sequence was added to the 5' side, and Spe I recognition sequence was added to the 3' side.
[SEQ ID NO: 16] shows riboprobe used to determine the quantity of SLC-1mRNA expressed in each clone of human SLC-1(S) expression CHO cells and SLC-1(L) expression CHO cells.

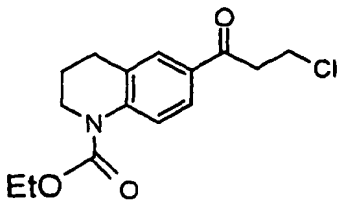
Transformant Escherichia coli DH10B/phSLC1L8 transformed by plasmid containing DNA which codes the base sequence shown by SEQ ID NO: 9, obtained in Reference Example 1 - 6, has been deposited with National Institute of Bioscience and Human-Technology (NIBH), Agency of Industrial Science and Technology, Ministry of International Trade and Industry, under accession of number FERM BP-6632 since February 1, 1999; and with the Institute for Fermentation, Osaka, Japan (IFO), under accession number of IFO 16254 since January 21, 1999.

Examples

Reference Example 1

Ethyl 6-(3-chloropropanoyl)-3,4-dihydro-1(2H)-quinoline carboxylate

[0379]



[0380] Aluminum chloride (23.5 g, 176 mmol) was added to a solution of ethyl 3,4-dihydro-1(2H)-quinoline carboxylate (14.5 g, 70.4 mmol) and 3-chloropropionyl chloride (7.39 ml, 77.4 mmol) in dichloromethane under cooling with water-bath, and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into iced water and extracted with dichloromethane. The extract was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The resulting residues were purified by silica gel column chromatography (developing solvent; hexane : ethyl acetate = 3 : 1) and crystallized from

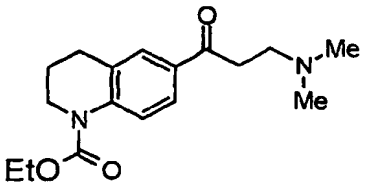
hexane, whereby the title compound (15.6 g) was obtained as colorless powder with a mp. of 78 to 79 °C.
^{1}H NMR ($CDCl_3$) δ 1.35 (3H, t, J = 7.0 Hz), 1.93 (2H, m), 2.83 (2H, t, J = 6.2 Hz), 3.42 (2H, t, J = 7.0 Hz), 3.81 (2H, t, J = 6.2 Hz), 3.92 (2H, t, J = 7.0 Hz), 4.28 (2H, q, J = 7.0 Hz), 7.74 (2H, m), 7.92 (1H, d, J = 8.8 Hz).

Elemental analysis for $C_{15}H_{18}ClNO_3$			
Calcd.	C, 60.91;	H, 6.13;	N, 4.74.
Found	C, 61.20;	H, 6.05;	N, 4.74.

Reference Example 2

Ethyl 6-[3-(dimethylamino)propanoyl]-3,4-dihydro-1 (2H)-quinoline carboxylate

[0381]

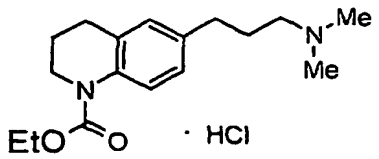


[0382] 50% Aqueous dimethylamine (51 mL) was added to a solution of ethyl 6-(3-chloropropanoyl)-3,4-dihydro-1 (2H)-quinoline carboxylate (15.0 g, 50.7 mmol) obtained in Reference Example 1 in dichloromethane at room temperature and then stirred for 2 hours. The reaction solution was separated, and the organic layer was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The resultant residues were purified by alumina column chromatography (developing solvent; hexane : ethyl acetate = 1 : 1), whereby the title compound (16.3 g) was obtained as pale yellow matter.
^{1}H NMR ($CDCl_3$) δ: 1.34 (3H, t, J = 7.0 Hz), 1.96 (2H, m), 2.29 (6H, s), 2.79 (4H, m), 3.11 (2H, m), 3.79 (2H, m), 4.24 (2H, q, J = 7.0 Hz), 7.72-7.78 (2H, m), 7.78 (1H, d, J = 8.4 Hz).

Reference Example 3

Ethyl 6-[3-(dimethylamino)propyl]-3,4-dihydro-1(2H)-quinoline carboxylate hydrochloride

[0383]



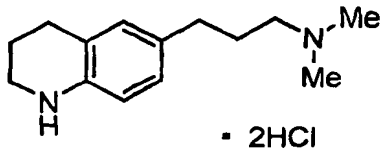
[0384] Triethyl silane (64.8 ml, 406 mmol) was added under a nitrogen atmosphere to a solution of ethyl 6-[3-(dimethylamino)propanoyl]-3,4-dihydro-1(2H)-quinoline carboxylate (15.4 g, 50.7 mmol) obtained in Reference Example 2 in trifluoroacetic acid and then stirred at room temperature for 5 days. The solvent was distilled away under reduced pressure, and ether was added to the residues which were then extracted with water. The aqueous layer was made basic with 8 N aqueous sodium hydroxide and then extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The resultant residues were purified by alumina column chromatography (developing solvent; hexane : ethyl acetate = 3 : 1). 4 N hydrogen chloride-ethyl acetate was added to a solution of the resultant oily matter in ether, and the formed solids were washed with diethyl ether, whereby the title compound (14.8 g) was obtained as hygroscopic colorless powder.
^{1}H NMR ($CDCl_3$, free base) δ: 1.32 (3H, t, J = 7.0 Hz), 1.78 (2H, m), 1.83 (2H, m), 2.22 (6H, s), 2.29 (2H, m), 2.56 (2H,

m), 2.75 (2H, t, J = 6.6 Hz), 3.74 (2H, m), 4.24 (2H, q, J = 7.0 Hz), 6.98 (2H, m), 7.59 (1H, d, J = 8.4 Hz).

Reference Example 4

N,N-Dimethyl-3-(1,2,3,4-tetrahydro-6-quinolinyl)-1-propan amine dihydrochloride

[0385]



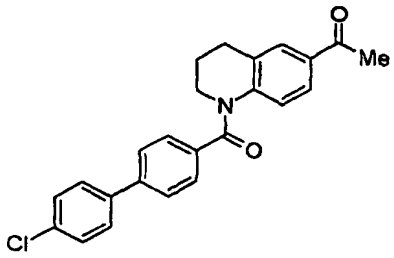
[0386] A solution of ethyl 6-[3-(dimethylamino)propyl]-3,4-dihydro-1(2H)-quinoline carboxylate hydrochloride (14.5 g, 44.4 mmol) obtained in Reference Example 3 in concd. hydrochloric acid (200 mL) was stirred at 120 °C for 16 hours, and the solvent was distilled away under reduced pressure and dried under reduced pressure, whereby the title compound (12.8 g) was obtained as hygroscopic powder with a mp. of 250 °C (decomp.).
^{1}H NMR (D_2O) δ 1.78 (4H, m), 2.41 (2H, t-like), 2.54 (6H, s), 2.60 (2H, t-like), 2.81 (2H, m), 3.22 (2H, m), 6.93 (3H, m).

Elemental analysis for $C_{14}H_{22}N_2 \cdot 2HCl$			
Calcd.	C, 57.73;	H, 8.31;	N, 9.62.
Found	C, 57.44;	H, 8.22;	N, 9.47.

Reference Example 5

1-[1-(4'-Chloro[1,1'-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl] ethanone

[0387]



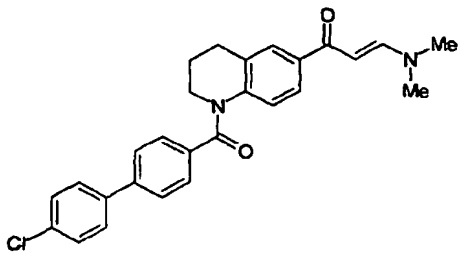
[0388] Oxalyl chloride (0.39 mL) and N,N-dimethylformamide (1 drop) were added in this order to a suspension of 4-(4-chlorophenyl)benzoic acid (1.05 g) in tetrahydrofuran (15 mL). After the mixture was stirred at room temperature for 1 hour, the solvent was distilled away under reduced pressure. The resultant residues were dissolved in tetrahydrofuran (10 mL) and then added to a suspension of 6-acetyl-1,2,3,4-tetrahydroquinoline (0.7 g), sodium hydroxide powder (0.31 g) and tetrabutyl ammonium hydrogensulfate (12 mg) in tetrahydrofuran (15 mL). After the mixture was stirred at room temperature for 3 hours, water was added to the reaction solution which was then extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The resultant residues were crystallized from diethyl ether, whereby the title compound (1.1g) was obtained as colorless crystals with a mp of 149 to 151 °C.
^{1}H NMR ($CDCl_3$) δ: 2.03-2.15 (2H, m), 2.53 (3H, s), 2.94 (2H, t, J=6.4 Hz), 3.95 (2H, t, J=6.3 Hz), 6.87 (1H, d, J=8.6 Hz), 7.38-7.61 (9H, m).7.79 (1H, s).

Elemental analysis for $C_{24}H_{20}ClNO_2$			
Calcd.	C, 73.94;	H, 5.17;	N, 3.59.
Found	C, 73.79;	H, 5.13;	N, 3.57.

Reference Example 6

(E)-1-[1-[(4'-Chloro[1,1'-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-3-(dimethylamino)-2-propen-1-one

[0389]



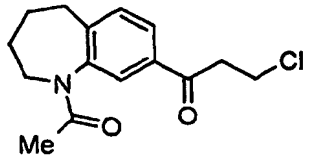
[0390] A mixture of 1-[1-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-1-quinolinyl] ethanone (0.65 g) obtained in Reference Example 5 and N,N-dimethylformamide dimethylacetal (8 ml) was stirred at 110 °C for 16 hours. The reaction solution was cooled to room temperature, then concentrated under reduced pressure and purified by alumina column chromatography (developing solvent; ethyl acetate). The resultant residues were crystallized from diethyl ether, whereby the title compound (1.1 g) was obtained as colorless crystals with a mp of 168 to 170 °C.
^{1}H NMR ($CDCl_3$) δ: 2.00-2.15 (2H, m), 2.75-3.20 (8H, m), 3.95 (2H, t, J=6.4 Hz), 5.64 (1H, d, J=12.3 Hz), 6.76 (1H, d, J=8.4 Hz), 7.37-7.53 (9H, m) 7.75-7.82 (2H, m).

Elemental analysis for $C_{27}H_{25}ClN_2O_2$			
Calcd.	C, 72.88;	H, 5.66;	N, 6.30.
Found	C, 72.58;	H, 5.84;	N, 6.20.

Reference Example 7

1-(1-Acetyl-2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-3-chloro-1-propanone

[0391]



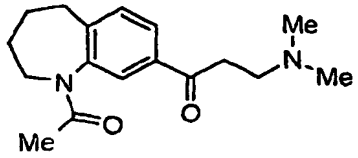
[0392] Aluminum chloride (30.8 g, 231 mmol) was added to a solution of 1-acetyl-2,3,4,5-tetrahydro-1H-1-benzazepine (17.5 g, 92.5 mmol) and 3-chloropropionyl chloride (13.2 ml, 139 mmol) in dichloroethane under cooling with water-bath, and then the mixture was stirred at 50 °C for 1 day. The reaction solution was poured into iced water and extracted with dichloromethane. The extract was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The resultant residues were purified by silica gel column chromatography (developing solvent; hexane : ethyl acetate = 1 : 1) and crystallized from hexane, whereby the title compound (8.47 g) was obtained as colorless powder with a mp. of 106 to 107 °C.

^{1}H NMR ($CDCl_3$) δ: 1.41 (1H, m), 1.87 (3H, s), 1.87-2.08 (3H, m), 2.54-2.83 (3H, m), 3.44 (2H, m), 3.93 (2H, m), 4.74 (1H, m), 7.38 (1H, d, J = 8.0 Hz), 7.76 (1H, s), 7.84 (1H, d, J = 8.0 Hz).

Reference Example 8

1-(1-Acetyl-2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-3-(dimethylamino)-1-propanone

[0393]



[0394] 50 % aqueous dimethylamine (27 ml) was added to a solution of 1-(1-acetyl-2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-3-chloro-1-propanone (7.10 g, 25.4 mmol) obtained in Reference Example 7 in dichloromethane at room temperature, and then stirred for 4 hours. After the reaction solution was separated, the organic layer was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The resultant residues were purified by alumina column chromatography (developing solvent; hexane : ethyl acetate = 1 : 1) and crystallized from hexane, whereby the title compound (5.38 g) was obtained as colorless powder with a mp. of 68 to 70 °C.

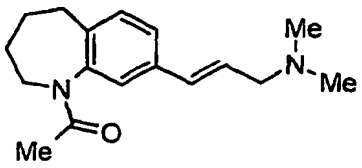
^{1}H NMR ($CDCl_3$) δ: 1.40 (1H, m) , 1.86 (3H, s), 1.81-2.07 (3H, m), 2.29 (6H, s), 2.59 (1H, m), 2.77 (4H, m), 3.13 (2H, m), 4.69 (1H, m), 7.36 (1H, d, J = 8.0 Hz), 7.75 (1H, d, J = 1.8 Hz), 7.83 (1H, dd, J = 1.8, 8.0 Hz).

Elemental analysis for $C_{17}H_{24}N_2O_2$			
Calcd.	C, 70.80;	H, 8.39;	N, 9.71.
Found	C, 70.87;	H, 8.16;	N, 9.44.

Reference Example 9

(E)-3-(1-Acetyl-2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-N,N-dimethyl-2-propen-1-amine

[0395]



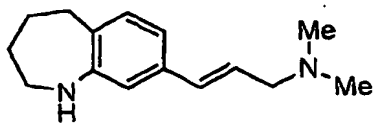
[0396] Triethyl silane (22.2 ml, 139 mmol) was added under a nitrogen atmosphere to a solution of 1-(1-acetyl-2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-3-(dimethylamino)-1-propanone (5.00 g, 17.3 mmol) obtained in Reference Example 8 in trifluoroacetic acid, and then the mixture was stirred at room temperature for 5 days. After the solvent was distilled away under reduced pressure, ether was added to the residues which were then extracted with water. The aqueous layer was made basic with 8 N aqueous sodium hydroxide and then extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The resultant residues were purified by alumina column chromatography (developing solvent; hexane : ethyl acetate =1 : 1), whereby the title compound (2.74 g) was obtained as oily matter.

^{1}H NMR ($CDCl_3$) δ: 1.39 (1H, m), 1.73-2.05 (5H, m), 2.28 (6H, s), 2.53-2.75 (4H, m), 3.08 (2H, dd, J = 0.8, 6.6 Hz), 4.69 (1H, m), 6.24 (1H, dt, J = 6.6, 16.0 Hz), 6.48 (1H, d, J = 16.0 Hz), 7.12-7.27 (3H, m).

Reference Example 10

(E)-N,N-Dimethyl-3-(2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-2-propen-1-amine

[0397]



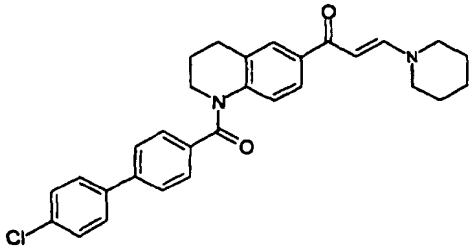
[0398] A solution of (E)-3-(1-acetyl-2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl)-N,N-dimethyl-2-propene-1-amine (2.73 g, 9.95 mmol) obtained in Reference Example 9 in concd. hydrochloric acid was stirred at 120 °C for 12 hours. After the solvent was distilled away under reduced pressure, the residues were made basic with 8 N aqueous sodium hydroxide and extracted with ethyl acetate. After the extract was washed with a saturated saline solution and dried over anhydrous sodium sulfate, the solvent was distilled away under reduced pressure, and the residues were crystallized from hexane, whereby the title compound (1.49 g) was obtained as colorless powder with a mp. of 87 to 88 °C. ^{1}H NMR ($CDCl_3$) δ: 1.63 (2H, m) , 1.78 (2H, m), 2.26 (6H, s), 2.74 (2H, m), 3.04 (4H, m), 3.78 (1H, br), 6.18 (1H, dt, J = 6.6, 16.0 Hz), 6.42 (1H, d, J = 16.0 Hz), 6.75 (1H, d, J = 1.6 Hz), 6.85 (1H, dd, J = 1.6, 7.8 Hz), 7.04 (1H, d, J = 7.8 Hz).

Elemental analysis for $C_{15}H_{22}N_2$			
Calcd.	C, 78.21;	H, 9.63;	N, 12.16.
Found	C, 78.15;	H, 9.73;	N, 12.23.

Reference Example 11

(E)-1-[1-[(4'-Chloro[1,1'-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-3-piperidino-2-propen-1-one

[0399]

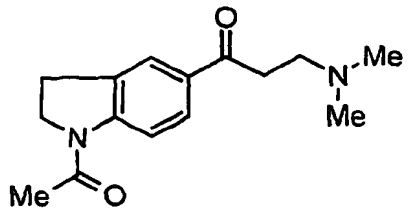


[0400] A mixture of (E)-[1-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-3-(dimethylamino)-2-propen-1-one (0.29 g) obtained in Reference Example 6 and piperidine (3 ml) was stirred at 110 °C for 2 hours. The reaction solution was cooled to room temperature, concentrated under reduced pressure and purified by alumina column chromatography (developing solvent; ethyl acetate). The resultant residues were crystallized from diethyl ether, whereby the title compound (0.28 g) was obtained as colorless crystals with a mp of 167 to 170 °C.
^{1}H NMR ($CDCl_3$) δ: 1.57-1.70 (6H, m), 2.03-2.15 (2H, m), 2.92 (2H, t, J=6.6 Hz), 3.25-3.45 (4H, m), 3.95 (2H, t, J=6.4 Hz), 5.74 (1H, d, J=12.5 Hz), 6.74 (1H, d, J=8.4 Hz), 7.37-7.61 (9H, m) 7.72-7.78 (2H, m).

Reference Example 12

1-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-3-(dimethylamino)-1-propanone

[0401]

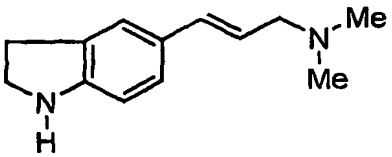


[0402] Using 1-acetyl indoline, the title compound was obtained as viscous oily matter by the same procedures as in Reference Examples 1 and 2.
^{1}H NMR ($CDCl_3$) δ: 2.21-2.33 (9H, m), 2.74 (2H, t, J=7.2 Hz), 3.11 (2H, t, J=7.2 Hz), 3.23 (2H, t, J=8.6 Hz), 4.12 (2H, t, J=8.6 Hz), 7.78-7.97 (2H, m) 8.24 (1H, d, J=8.4 Hz).

Reference Example 13

(E)-3-[2,3-Dihydro-1H-indol-5-yl]-N,N-dimethyl-2-propene-1-amine

[0403]



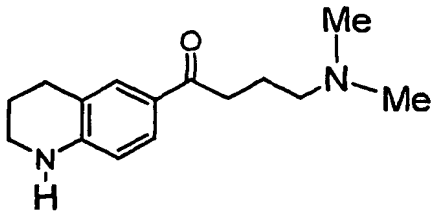
1) Sodium borohydride (0.75 g) was added to a solution of 1-(1-acetyl-2,3-dihydro-1H-indol-5-yl)-3-(dimethylamino)-1-propanone (4.3 g) obtained in Reference Example 12 in methanol (40 ml) under cooling with ice-bath, and the mixture was stirred at 0 to 5 °C for 30 minutes. After iced water was added to the reaction solution, the solvent was distilled away under reduced pressure, and the residues were extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The resultant residues were purified by alumina column chromatography (developing solvent; ethyl acetate), whereby 3-[1-acetyl-2,3-dihydro-1H-indol-5-yl]-3-hydroxy-N,N-dimethyl-1-propanamine (3.3 g) was obtained as colorless powder.
2) A mixture of 3-[1-acetyl-2,3-dihydro-1H-indol-5-yl]-3-hydroxy-N,N-dimethyl-1-propanamine (3.3 g) obtained in 1) above and concd. hydrochloric acid (20 ml) was heated for 16 hours under reflux. The reaction solution was cooled to room temperature, then concentrated under reduced pressure, diluted with water, made basic with 2 N aqueous sodium hydroxide and extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure, whereby the title compound (2.3 g) was obtained as oily matter.

^{1}H NMR ($CDCl_3$) δ: 2.25 (6H, s), 2.97-3.04 (4H, m), 3.55 (2H, t, J=8.2 Hz), ca. 3.8 (1H, br.s, NH), 5.98-6.09 (1H, m), 6.41 (1H, d, J=16.2 Hz), 6.56 (1H, d, J=8.1 Hz), 7.02 (1H, dd, J=1.5, 8.1 Hz), 7.19 (1H, s).

Reference Example 14

1-(1,2,3,4-Tetrahydro-6-quinolinyl)-4-(dimethylamino)-1-butanone

[0404]

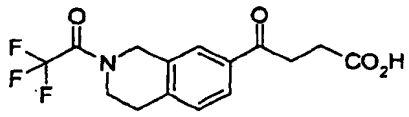


[0405] Using ethyl 3,4-dihydro-1(2H)-quinoline carboxylate, the title compound was obtained as viscous oily matter by the same procedures as in Reference Examples 1, 2 and 4.
^{1}H NMR ($CDCl_3$) δ: 1.87-2.00 (4H, m), 2.33 (6H, s), 2.48 (2H, t, J = 7.4 Hz), 2.78 (2H, t, J = 6.3 Hz), 2.91 (2H, t, J = 7.2 Hz), 3.37 (2H, t, J = 5.6 Hz), 4.4 (1H, br, NH), 6.39 (1H, d, J = 9.2 Hz), 7.60-7.64 (2H, m).

Reference Example 15

4-Oxo-4-[2-(trifluoroacetyl)-1,2,3,4--tetrahydro-7-isoquinolinyl]butanoic acid

[0406]

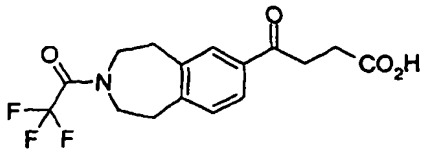


1) Trifluoroacetic anhydride (47.5 ml, 336 mmol) was added dropwise to a solution of 1,2,3,4-tetrahydroisoquinoline (25 g, 188 mmol) in THF (100 ml) at 0°C and stirred for 2 hours at room temperature, and then the solvent was distilled away under reduced pressure. Water was poured into the residues which were then extracted with ethyl acetate, washed with 1 N hydrochloric acid, and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, whereby 43.5 g of 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline was obtained as oily matter.
^{1}H-NMR ($CDCl_3$) δ: 3.00-2.93 (2H, m), 3.92-3.80 (2H, m), 4.77 (2H, m), 7.28-7.13 (4H, m).
2) Aluminum chloride (26 g, 200 mmol) was added little by little to a mixture of 2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline (10 g, 43.6 mmol) obtained in 1) above and succinic anhydride (4.8 g, 48 mmol) in dichloroethane at room temperature, and the mixture was stirred at 45 °C for 1 hour. The reaction solution was poured into iced water, extracted with ethyl acetate, washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, and the residues were purified by silica gel column chromatography (developing solvent; hexane : ethyl acetate = 1 : 1), whereby 7.5 g of the title compound was obtained as colorless powder.
^{1}H-NMR (DMSO-d_6) δ: 2.58 (2H, m), 3.00 (2H, m), 3.23 (2H, m), 3.83 (2H, m), 4.84 (2H, m), 7.38 (1H, m), 7.84 (1H, m), 7.93 (1H, m), 12.17 (1H, s).

Reference Example 16

4-Oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanoic acid

[0407]

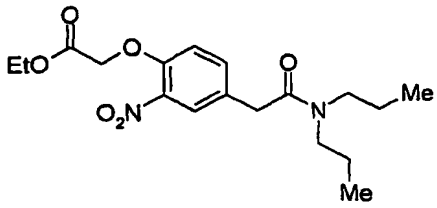


[0408] Using 2,3,4,5-tetrahydro-1H-3-benzazepine, the title compound was obtained as colorless powder by the same procedure as in Reference Example 15.
^{1}H-NMR ($CDCl_3$) δ: 2.81 (2H, t, J=6.4Hz), 2.90-3.15 (4H, m) , 3.29 (2H, t, J=6.4Hz), 3.65-3.85 (4H, m), 7.20-7.33 (1H, m), 7.75-7.85 (2H, m), ca. 10 (1H, br) .

Reference Example 17

N,N-Dipropyl-(4-ethoxycarbonylmethoxy-3-nitrophenyl) acetamide

[0409]



1) A solution of nitric acid (24.5 ml, 398 mmol) in acetic acid (20 ml) was slowly added dropwise under cooling with ice-bath to a solution of (4-hydroxyphenyl)acetic acid (50.4 g, 330 mmol) in acetic acid (230 ml) such that the temperature of the reaction solution did not exceed 10 °C. After the reaction solution was stirred for 2 hours, water (1 L) was added dropwise thereto and the precipitated crystals were collected by filtration. The resultant crystals were washed with water and dried, whereby (4-hydroxy-3-nitrophenyl)acetic acid (49 g) was obtained as crystals with a mp of 144 to 146 °C.
^{1}H-NMR ($CDCl_3$) δ: 3.76 (2H, s), 7.16 (1H, d, J = 8.8 Hz), 7.53 (1H, dd, J = 8.8, 2.2 Hz), 8.04 (1H, d, J = 2.2 Hz).
2) Thionyl chloride (50 ml, 680 mmol) was added dropwise to a solution of (4-hydroxy-3-nitrophenyl)acetic acid (25 g, 127 mmol) obtained in 1) in THF (100 ml) at room temperature, and the mixture was heated under reflux for 2 hours. The reaction solution was concentrated, and the resultant residues were dissolved in chloroform (250 ml) and added dropwise over 1 hour to a solution of dipropylamine (35 ml, 255 mmol) in chloroform (300 ml) under cooling with ice-bath. After this addition, the reaction solution was washed with water and aqueous saturated sodium bicarbonate, and the organic layer was dried over anhydrous sodium sulfate and concentrated. The residues were crystallized from ethyl acetate-hexane, whereby N,N-dipropyl-(4-hydroxy-3-nitrophenyl) acetamide (26.5 g) was obtained as crystals with a mp of 55 to 57 °C.
^{1}H-NMR ($CDCl_3$) δ: 0.8-1.0 (6H, m), 1.4-1.7 (4H, m), 3.2-3.4 (4H, m), 3.67 (2H, s), 7.12 (1H, d, J = 8.6 Hz), 7.53 (1H, dd, J = 8.6, 2.2 Hz), 7.96 (1H, d, J = 2.2 Hz).
3) Potassium carbonate (7.4 g, 53 mmol) was added to a solution of N,N-dipropyl-(4-hydroxy-3-nitrophenyl) acetamide (3.5 g, 17.8 mmol) obtained in 2) above and ethyl bromoacetate (3.0 ml, 26.7 mmol) in DMF (40 ml). After the reaction solution was stirred overnight at room temperature, water was added to the reaction solution which was then extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated. The residues were recrystallized from ethyl acetate-hexane, whereby the title compound (4.9 g, 75 %) was obtained as crystals with a mp of 79 to 80 °C.

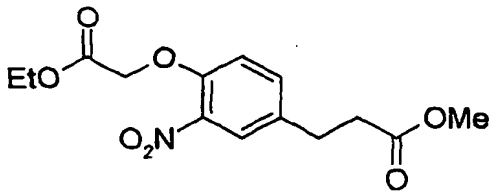
^{1}H-NMR ($CDCl_3$) δ: 0.8-1.0 (6H, m), 1.29 (3H, t, J = 7.0 Hz), 1.4-1.7 (4H, m) , 3.1-3.4 (4H, m), 3.68 (2H, s), 4.27 (2H, q, J = 7.0 Hz), 4.76 (2H, s), 6.96 (1H, d, J = 8.6 Hz), 7.38 (1H, dd, J = 8.6, 2.2 Hz), 7.77 (1H, d, J = 2.2 Hz).

Elemental analysis for $C_{18}H_{26}N_2O_6$			
Calcd.	C, 59.00;	H, 7.15;	N, 7.65.
Found	C, 58.92;	H, 7.15;	N, 7.85.

Reference Example 18

Methyl 3-(4-ethoxycarbonylmethoxy-3-nitrophenyl)propionate

[0410]

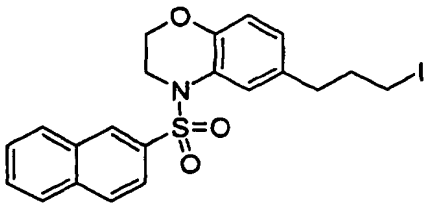


1) Using 3-(4-hydroxyphenyl)propionic acid, 3-(4-hydroxy-3-nitrophenyl)propionic acid was obtained as powder by the same procedure as in 1) in Reference Example 17.
^{1}H-NMR ($CDCl_3$) δ: 2.70 (2H, t, J = 7.4 Hz), 2.95 (2H, t, J = 7.4 Hz), 7.10 (1H, d, J = 8.8 Hz), 7.46 (1H, dd, J = 8.8, 2.0 Hz), 7.96 (1H, d, J = 2.0 Hz).
Melting point: 80-82 °C (crystallizing solvent: ethyl acetate-hexane)
2) Thionyl chloride (15 ml) was added dropwise to a solution of 3-(4-hydroxy-3-nitrophenyl)propionic acid (49 g, 232 mmol) obtained in 1) above in methanol (500 ml), and the mixture was stirred overnight at room temperature. After, the reaction solution was concentrated, water (500 ml) was added to the reaction solution which was then extracted with ethyl acetate. The extract was washed with water and aqueous saturated sodium bicarbonate, dried over magnesium sulfate and concentrated, whereby methyl 3-(4-hydroxy-3-nitrophenyl)propionate (47 g) was obtained as powder.
^{1}H-NMR ($CDCl_3$) δ: 2.64 (2H, t, J = 7.4Hz), 2.95 (2H, t, J = 7.4Hz), 3.68 (3H, s), 7.10 (1H, d, J = 8.6Hz), 7.46 (1H, dd, J = 8.6, 2.2Hz), 7.95 (1H, d, J = 2.2 Hz).
Melting point: 60-62 °C (crystallizing solvent: ethyl acetate-hexane)
3) Using methyl 3-(4-hydroxy-3-nitrophenyl)propionate obtained in 2) above, the title compound was obtained as powder by the same procedure as in 3) in Reference Example 17.
^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J = 7.0Hz), 2.64 (2H, t, J = 7.4Hz), 2.95 (2H, t, J = 7.4Hz), 3.67 (3H, s), 4.26 (2H, q, J = 7.0Hz), 4.75 (2H, s), 6.93 (1H, d, J = 8.6Hz), 7.38 (1H, dd, J = 8.6, 2.2Hz), 7.72 (1H, d, J = 2.2Hz).
Melting point: 70-72 °C (crystallizing solvent: ethyl acetate-hexane)

Reference Example 19

3,4-Dihydro-6-(3-iodopropyl)-4-(2-naphthalenesulfonyl)-2H-1,4-benzoxazine

[0411]

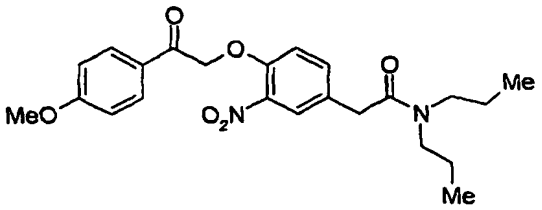


1) Using methyl 3-(4-ethoxycarbonylmethoxy-3-nitrophenyl)propionate obtained in Reference Example 18, methyl 3-(3,4-dihydro-2H-1,4-benzoxazine-3-oxo-6-yl)propionate was obtained as powder by the same procedure as in Example 133.
^{1}H-NMR ($CDCl_3$) δ: 2.60 (2H, t, J = 7.4 Hz), 2.88 (2H, t, J = 7.4 Hz), 3.68 (3H, s), 4.59 (2H, s), 6.7-7.0 (3H, m).
Melting point: 131-132 °C (crystallizing solvent: ethyl acetate-hexane)
2) 1 N borane/THF solution (150 ml, 150 mmol) was added to a solution of methyl 3-(3,4-dihydro-2H-1,4-benzoxazine-3-oxo-6-yl)propionate (24 g, 102 mmol) obtained in 1) above in THF (400 ml) under cooling with ice-bath. The reaction solution was stirred overnight at room temperature, then 6 N hydrochloric acid (50 ml, 300 mmol) was added to the reaction solution which was then stirred for 2 hours, neutralized with 6 N aqueous sodium hydroxide and extracted with ethyl acetate. The extract was washed with water and a saturated saline solution, dried over magnesium sulfate, and concentrated. After triethylamine (25 g, 250 mmol) was added to a solution of the residues in acetonitrile (300 ml), a solution of 2-naphthalene sulfonyl chloride (56 g, 250 mmol) in acetonitrile (100 ml) was added thereto under cooling with ice-bath and stirred at room temperature for 4 hours. The reaction solution was concentrated, and water was added to the residues which were then extracted with ethyl acetate. The extract was washed with water and a saturated saline solution, dried over magnesium sulfate and concentrated. Sodium iodide (37.5 g, 250 mmol) was added to a solution of the residues in acetone (500 ml), and the mixture was stirred overnight at room temperature. The reaction solution was concentrated, and water (500 ml) was added to the concentrate which was then extracted with ethyl acetate. The extract was washed with water and a saturated saline solution, dried over magnesium sulfate and concentrated, whereby the title compound (22 g) was obtained as powder.
^{1}H-NMR ($CDCl_3$) δ: 2.0-2.2 (2H, m) , 2.71 (2H, t, J = 7.4 Hz), 3.18 (2H, t, J = 7.2 Hz), 3.72 (2H, t, J = 4.6 Hz), 3.93 (2H, t, J = 4.6 Hz), 6.70 (1H, d, J = 8.0 Hz), 6.90 (1H, dd, J = 8.0, 1.8 Hz), 7.5-7.8 (4H, m), 7.8-8.0 (3H, m), 8.30 (1H, s).
Melting point: 87-88 °C (crystallizing solvent: ethyl acetate-hexane)

Reference Example 20

N,N-Dipropyl-[4-(4-methoxyphenyl)carbonylmethoxy-3-nitrophenyl]acetamide

[0412]



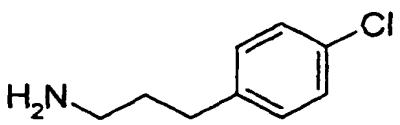
[0413] Using N,N-dipropyl-(4-hydroxy-3-nitrophenyl)acetamide obtained in 2) in Reference Example 17, the title

compound was obtained as powder by the same procedure as in 3) in Reference Example 17.
^{1}H-NMR ($CDCl_3$) δ: 0.8-1.0 (6H, m) , 1.4-1.7 (4H, m) , 3.1-3.4 (4H, m), 3.65 (2H, s), 3.89 (3H, s), 5.34 (2H, s), 6.9-7.1 (3H, m), 7.40 (1H, dd, J = 8.6, 2.2 Hz), 7.76 (1H, d, J = 2.2 Hz), 8.00 (2H, d, J = 9.0 Hz).
Melting point: 95-97 °C (crystallizing solvent: ethyl acetate-hexane)

Reference Example 21

3-(4-Chlorophenyl)propylamine

[0414]

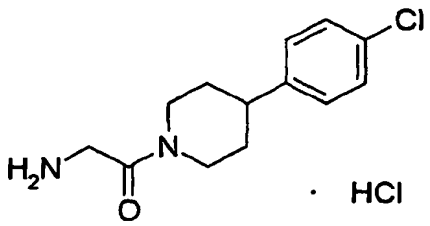


1) After a mixture of 3-(4-chlorophenyl)propionic acid (5.00 g, 27.0 mmol) and thionyl chloride (3 ml) was refluxed for 2 hours, an excess of the thionyl chloride was distilled away under reduced pressure. The resultant residues were dissolved in tetrahydrofuran (200 ml), dropped slowly to a suspension of $LiA1H_4$ in tetrahydrofuran at 0 °C and stirred at room temperature for 1 hour. Water and 1 N aqueous sodium hydroxide were added to the reaction mixture, and after insolubles were filtered off, the filtrate was dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, whereby 4.6 g 3-(4-chlorophenyl)propyl alcohol was obtained as oily matter.
^{1}H-NMR ($CDCl_3$) δ: 1.86 (2H, tt, J = 7.4, 7.4 Hz), 2.68 (2H, t, J = 7.4 Hz), 3.67 (2H, t, J = 7.4 Hz), 7.12 (2H, d, J = 8.4 Hz), 7.27 (2H, d, J = 8.4 Hz).
2) Mesyl chloride (2.10 ml, 27.1 mmol) was added to a solution of 3-(4-chlorophenyl)propyl alcohol (4.6 g, 27 mmol) obtained in 1) above and triethylamine (3.78 ml, 27.1 mmol) in tetrahydrofuran (100 ml) at 0 °C and stirred at room temperature for 30 minutes. Water was added to the reaction mixture which was then extracted with ethyl acetate. The extract was washed with an aqueous saturated NaCl solution and dried over anhydrous magnesium sulfate. After the solvent was distilled away under reduced pressure, the reaction mixture and potassium phthalimide (5.02 g, 27.1 mmol) were dissolved in dimethylformamide and heated at 80 °C for 10 hours under stirring. 8 N aqueous sodium hydroxide was added to the resultant solution which was then extracted with ethyl acetate. The extract was washed with an aqueous saturated NaCl solution and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, whereby 7.47 g 2-[3-(4-chlorophenyl)propyl]-1H-isoindole-1,3(2H)-dione was obtained as solid.
^{1}H-NMR ($CDCl_3$) δ: 2.00 (2H, tt, J = 7.4, 7.4 Hz), 2.69 (2H, t, J = 7.4 Hz), 3.73 (2H, t, J = 7.4 Hz), 7.10-7.82 (4H, m), 7.69-7.89 (4H, m).
3) A solution of 2-[3-(4-chlorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (7.47 g, 24.8 mmol) obtained in 2) above and hydrazine monohydrate (2.4 ml, 49.7 mmol) in ethanol was heated for 10 hours under reflux. After the solvent was distilled away, water was added to the residues which were then extracted with ethyl acetate. The extract was washed with an aqueous saturated NaCl solution and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, whereby 3.66 g of the title compound was obtained as oily matter.
^{1}H-NMR ($CDCl_3$) δ: 1.80 (2H, tt, J = 7.4, 7.4 Hz), 2.63 (2H, t, J = 7.4 Hz), 2.76 (2H, t, J = 7.4 Hz), 3.08 (2H, s) , 7.08-7.29 (4H, m).

Reference Example 22

2-[4-(4-Chlorophenyl)-1-piperidinyl]-2-oxoethylamine hydrochloride

[0415]

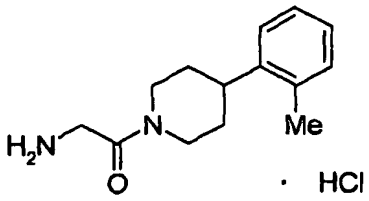


1) Diethyl cyanophosphate (1.29 ml) was added to a solution of 4-(4-chlorophenyl)-1-piperidine hydrochloride (1.80 g), N-(tert-butoxycarbonyl) glycine (1.49 g) and triethylamine (2.38 ml) in DMF (80 ml). The reaction mixture was stirred at room temperature for 4 hours, diluted with water and extracted with ether. The extract was washed with a saturated saline solution and dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The residues were purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/1), whereby tert-butyl-2-[4-(4-chlorophenyl)-1-piperidinyl]-2-oxoethyl carbamate (2.48 g) was obtained.
^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.50-1.70 (2H, m), 1.80-2.00 (2H, m), 2.60-2.90 (2H, m), 3.00-3.20 (1H, m), 3.75-3.90 (1H, m), 3.99 (2H, m), 4.70-4.80 (1H, m), 5.56 (1H, m), 7.11 (2H, d, J=8.4Hz), 7.29 (2H, d, J=8.4Hz).
2) tert-Butyl-2-[4-(4-chlorophenyl)-1-piperidinyl]-2-oxoethyl carbamate (2.48 g) obtained in 1) above was dissolved in 4 N hydrogen chloride in ethyl acetate (50 ml) and stirred at room temperature for 4 hours. The solvent was distilled away under reduced pressure, whereby the title compound (2.16 g) was obtained.
MS(ESI) (M+H): 253.
^{1}H-NMR ($CDCl_3$) δ: 1.40-2.00 (4H, m), 2.65-3.00 (2H, m), 3.05-3.20 (1H, m), 3.75-4.00 (3H, m), 4.40-4.60 (1H, m), 7.27 (2H, d, J=8.8Hz), 7.37 (2H, d, J=8.5Hz), 8.25 (2H, m).

Reference Example 23

2-[4-(2-Methylphenyl)-1-piperidinyl]-2-oxoethylamine hydrochloride

[0416]

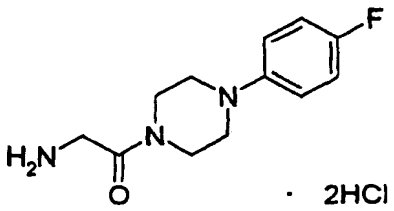


1) Using 4-(2-methylphenyl)-1-piperidine hydrochloride, tert-butyl-2-[4-(2-methylphenyl)-1-piperidinyl]-2-oxoethyl carbamate was obtained by the same procedure as in 1) in Reference Example 22.
^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 1.55-1.75 (2H, m), 1.80-1.90 (2H, m), 2.36 (3H, s), 2.60-2.80 (1H, m), 2.90-3.20 (2H, m), 3.75-3.90 (1H, m), 4.01 (2H, m), 4.70-4.85 (1H, m), 5.58 (1H, m), 7.00-7.20 (4H, m).
2) Using tert-butyl-2-[4-(2-methylphenyl)-1-piperidinyl]-2-oxoethyl carbamate obtained in 1) above, the title compound was obtained by the same procedure as in 2) in Reference Example 22.
MS(ESI) (M+H): 233.
^{1}H-NMR ($CDCl_3$) δ: 1.40-2.00 (4H, m), 2.32 (3H, s),2.70-2.91 (1H, m), 2.95-3.30 (2H, m), 3.75-4.00 (3H, m), 4.40-4.60 (1H, m), 7.10-7.30 (4H, m), 8.25 (2H, m).

Reference Example 24

2-[4-(4-Fluorophenyl)-1-piperazinyl]-2-oxoethylamine dihydrochloride

[0417]

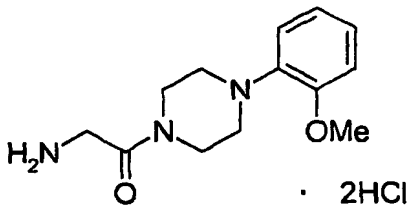


1) Using 1-(4-fluorophenyl) piperazine, tert-butyl-2-[4-(4-fluorophenyl)-1-piperazinyl]-2-oxoethyl carbamate was obtained by the same procedure as in 1) in Reference Example 22.
^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 3.05-3.15 (4H, m) , 3.55 (2H, t, J=5.1Hz), 3.79 (2H, t, J=5.1Hz), 4.01 (2H, d, J=4.5Hz), 5.52 (1H, m), 6.85-7.05 (4H, m).
2) Using tert-butyl-2-[4-(4-fluorophenyl)-1-piperazinyl]-2-oxoethyl carbamate obtained in 1) above, the title compound was obtained by the same procedure as in 2) in Reference Example 22.
MS(ESI) (M+H): 238.
^{1}H-NMR ($CDCl_3$) δ: 3.25-3.60 (4H, m), 3.70-4.00 (6H, m), 7.15-7.30 (3H, m), 7.30-7.50 (1H, m).

Reference Example 25

2-[4-(2-Methoxyphenyl)-1-piperazinyl]-2-oxoethylamine dihydrochloride

[0418]

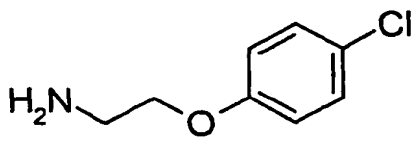


1) Using 1-(2-methoxyphenyl) piperazine, tert-butyl-2-[4-(2-methoxyphenyl)-1-piperazinyl]-2-oxoethyl carbamate was obtained by the same procedure as in 1) in Reference Example 22.
^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s), 3.00-3.07 (4H, m), 3.56 (2H, t, J=5.4Hz), 3.82 (2H, t, J=5.4Hz), 3.88 (3H, s), 4.01 (2H, d, J=4.5Hz), 5.56 (1H, m), 6.85-7.05 (4H, m).
2) Using tert-butyl-2-[4-(2-methoxyphenyl)-1-piperazinyl]-2-oxoethyl carbamate obtained in 1) above, the title compound was obtained by the same procedure as in 2) in Reference Example 22.
MS(ESI) (M+H) : 250.
^{1}H-NMR ($CDCl_3$) δ: 3.20-3.50 (4H, m), 3.75-4.10 (6H, m), 3.87 (3H, s), 7.01 (1H, t, J=8.0Hz), 7.15 (1H, d, J=8.0Hz), 7.27 (1H, t, J=8.0Hz), 7.49 (1H, d, J=8.0Hz).

Reference Example 26

2-(4-Chlorophenoxy)ethylamine

[0419]

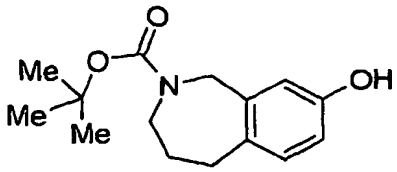


1) Sodium hydride (60 % in oil, 640 mg, 16 mmol) was added to a solution of 4-chlorophenol (2 g, 15.6 mmol) in dimethylformamide (20 ml) and stirred at room temperature for 30 minutes, and then N-(2-bromoethyl) phthalimide (4 g, 15.6 mmol) was added thereto and heated at 50 °C for 2 hours under stirring. After the solvent was distilled away under reduced pressure, water was added to the residues which were then extracted with ethyl acetate. The extract was washed with an aqueous saturated NaCl solution and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, whereby 1.00 g of 2-[3-(4-chlorophenoxy)ethyl]-1H-isoindole-1,3(2H)-dione was obtained as powder.
^{1}H-NMR ($CDCl_3$) δ: 4.10 (2H, t, J = 5.7 Hz), 4.18 (2H, t, J = 5.7 Hz), 7.10-7.82 (4H, m), 7.69-7.89 (4H, m).
2) Using 2-[3-(4-chlorophenoxy)ethyl]-1H-isoindole-1,3(2H)-dione obtained in 1) above, the title compound was obtained by the same procedure as in 3) in Reference Example 21.
^{1}H-NMR ($CDCl_3$) δ: 3.10 (2H, t, J = 5.4 Hz), 3.40 (2H, s), 3.98 (2H, t, J = 5.4 Hz), 6.82 (2H, d, J = 9.2 Hz), 7.24 (2H, d, J = 9.2 Hz).

Reference Example 27

tert-Butyl 8-hydroxy-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate

[0420]

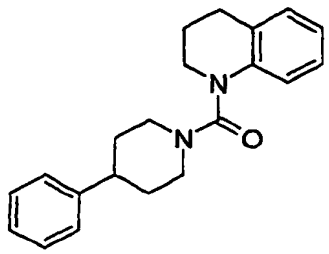


[0421] 2 N sodium hydroxide (40 ml) and t-butyl dicarbonate were added at 0 °C to a solution of 2,3,4,5-tetrahydro-1H-2-benzazepin-8-ol hydrobromate (12.0 g, 49.2 mm) in chloroform (40 ml) and water (40 ml), and the mixture was stirred at room temperature for 16 hours. Ethyl acetate was added to the resulting mixture which was then washed with a saturated saline solution and dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure, and the resultant residues were formed into powder with ethyl acetate-isopropyl ether, to give the title compound (7.99 g).
^{1}H NMR ($CDCl_3$) δ: 1.40 (9H, s), 1.73 (2H, m), 2.86 (2H, m), 3.67 (2H, m), 4.30-4.36 (2H, m), 6.61-6.70 (2H, m), 6.98 (1H, m).

Reference Example 28

1-[(4-Phenyl-1-piperidinyl)carbonyl]-1,2,3,4-tetrahydroquinoline

[0422]



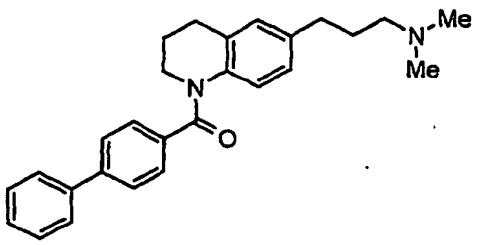
1) 1,2,3,4-Tetrahydroquinoline (1 ml, 7.97 mmol) was dissolved in THF (20 ml), and pyridine (1.58 ml, 15.93 mmol) was added thereto and cooled on ice. p-Nitrophenyl chloroformate (1.61 g, 7.97 mmol) was added to the reaction solution and stirred at room temperature for 4 hours, then water and a saturated saline solution were added, and the reaction solution was extracted with ethyl acetate. The extract was dried over magnesium sulfate and concentrated under reduced pressure, whereby 2.57 g 4-nitrophenyl 3,4-dihydroquinoline-1(2H)-carboxylate was obtained as pale yellow solution.

2) 4-Nitrophenyl 3,4-dihydroquinoline-1(2H)-carboxylate obtained in 1) above was dissolved in DMSO (10 ml), and 4-phenylpiperidine hydrochloride (1.58 g, 7.97 mmol) and 4 N aqueous sodium hydroxide (2.09 ml, 8.36 mmol) were added thereto and stirred at room temperature for 22.5 hours. 60 ml ethyl acetate was added to the reaction solution which was then washed with an aqueous potassium carbonate solution and a saturated saline solution. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure, and the resultant residues were purified by silica gel column chromatography (developing solvent; hexane : ethyl acetate = 2 : 1), whereby 2.10 g of the title compound was obtained as pale yellow liquid.
^{1}H-NMR ($CDCl_3$) δ: 1.68 (2H, m), 1.80 (2H, m), 1.98 (2H, m) , 2.65 (1H, m), 2.78 (2H, dd, J=6.6 and 6.9Hz), 2.85 (2H, m), 3.62 (2H, t, J=6.1Hz), 3.95 (2H, m), 6.90 (1H, m), 7.04-7.32 (8H, m).

Example 1

3-[1-([1,1'-Biphenyl]-4-ylcarbonyl)-1,2,3,4-tetrahydro-6-quinolinyl]-N,N-dimethyl-1-propanamine

[0423]



[0424] Biphenylcarbonyl chloride (327 mg, 1.51 mmol) was added to a solution of N,N-dimethyl-3-(1,2,3,4-tetrahydro-6-quinolinyl)-1-propanamine dihydrochloride (400 mg, 1.37 mmol) obtained in Reference Example 4 and triethylamine (669 ml, 4.81 mmol) in dimethylformamide under cooling with ice-bath, and the mixture was stirred at room temperature for 3 days. Ethyl acetate was added to the reaction solution which was then washed with an aqueous saturated sodium bicarbonate solution and a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The resultant residues were purified by alumina column chromatography (developing solvent; hexane : ethyl acetate = 3 : 1) and crystallized from hexane, whereby the title compound (113 mg)

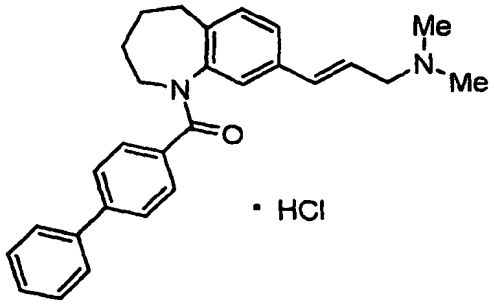
was obtained as colorless powder with a mp. of 100 to 101 °C.
^{1}H NMR ($CDCl_3$) δ: 1.73 (2H, m), 2.06 (2H, m), 2.20 (6H, s), 2.26 (2H, m), 2.54 (2H, m), 2.83 (2H, m), 3.92 (2H, t-like), 6.72 (2H, m), 6.99 (1H, s), 7.35-7.60 (9H, m).

Elemental analysis for $C_{27}H_{30}N_2O$			
Calcd.	C, 81.37;	H, 7.59;	N, 7.03.
Found	C, 81.26;	H, 7.46;	N, 7.05.

Example 2

(E)-3-[1-([1,1'-Biphenyl]-4-ylcarbonyl)-2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl]-N,N-dimethyl-2-propen-1-amine hydrochloride

[0425]



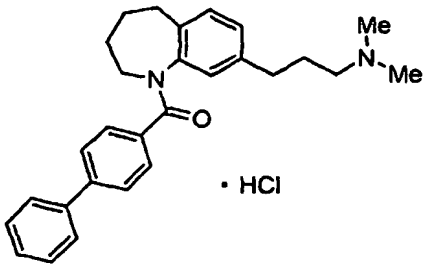
[0426] Biphenylcarbonyl chloride (423 mg, 1.95 mmol) was added to a solution of (E)-N,N-dimethyl-3-(2,3,4,5-tetrahydro-1 H-1-benzazepin-8-yl)-2-propene-1-amine (300 mg, 1.30 mmol) obtained in Reference Example 10, sodium hydroxide (130 mg, 3.26 mmol) and tetrabutylammonium hydrogensulfate (4.4 mg, 13.0 mmol) in tetrahydrofuran under cooling with ice-bath, and the mixture was stirred at room temperature for 5 hours. Ethyl acetate was added to the reaction solution which was then washed with a saturated saline solution and dried over anhydrous sodium sulfate, and the solvent was distilled away under reduced pressure. The resultant residues were purified by alumina column chromatography (developing solvent; hexane : ethyl acetate = 3 : 1). 4 N hydrogen chloride in ethyl acetate was added to the resultant oily matter, and the formed crystals were washed with diethyl ether, whereby the title compound (124 mg) was obtained as colorless powder with a mp. of 112 to 113 °C.
^{1}H NMR ($CDCl_3$, free base) δ: 1.53 (1H, m), 1.96 (2H, m), 2.15 (6H, s), 2.77-3.07 (6H, m), 5.04 (1H, m), 5.93 (1H, dt, J = 6.6, 15.8 Hz), 6.20 (1H, d, J = 15.8 Hz), 6.68 (1H, s), 7.02-7.51 (11H, m).

Elemental analysis for $C_{28}H_{30}N_2O \cdot HCl \cdot 1.5H_2O$			
Calcd.	C, 70.94;	H, 7.23;	N, 5.91.
Found	C, 71.40;	H, 7.31;	N, 6.11.

Example 3

3-[1-([1,1'-Biphenyl]-4-ylcarbonyl)-2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl]-N,N-dimethyl-1-propanamine hydrochloride

[0427]



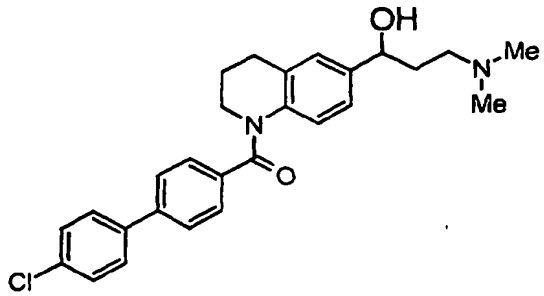
[0428] Palladium-carbon (200 mg) was added to a solution of (E)-3-[1-([1,1'-biphenyl]-4-ylcarbonyl)-2,3,4,5-tetrahydro-1H-1-benzazepin-8-yl]-N,N-dimethyl-2-propen-1-amine (238 mg, 0.580 mmol) obtained in Example 2 in tetrahydrofuran, and the mixture was stirred in a hydrogen atmosphere for 1.5 days. The catalyst was filtered off, and the solvent was distilled away under reduced pressure. The resultant residues were purified by alumina column chromatography (developing solvent; hexane : ethyl acetate = 3 : 1). 4 N hydrogen chloride in ethyl acetate was added to the resultant oily matter, and the formed crystals were washed with diethyl ether, whereby the title compound (97.9 mg) was obtained as colorless powder with a mp. of 84 to 86 °C. ^{1}H NMR ($CDCl_3$, free base) δ 1.35-1.52 (3H, m), 1.93-2.00 (10H, m), 2.33 (2H, m), 2.79-3.02 (4H, m), 5.04 (1H, m), 6.49 (1H, s), 6.89 (1H, m), 7.12 (1H, d, J = 7.8 Hz), 7.22-7.52 (9H, m).

Elemental analysis for $C_{28}H_{32}N_2O \cdot HCl \cdot H_2O$			
Calcd.	C, 72.01;	H, 7.55;	N, 6.00.
Found	C, 71.88;	H, 7.56;	N, 5.99.

Example 4

3-[1-([4'-Chloro[1,1-biphenyl]-4-yl)carbonyl)-1,2,3,4-tetrahydro-6-quinolinyl]-3-hydroxy-N,N-dimethyl-1-propanamine

[0429]



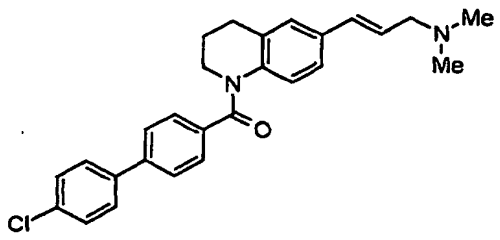
[0430] Sodium borohydride (0.6g) was added to a solution of (E)-[1-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-3-(dimethylamino)-2-propen-1-one (0.3 g) obtained in Reference Example 6 in methanol (30 ml), and the mixture was heated for 3 hours under reflux. After the solvent was distilled away under reduced pressure, the residues were dissolved in water-ethyl acetate and extracted with ethyl acetate. The extract was washed

with water and dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The resultant residues were purified by alumina column chromatography (developing solvent; ethyl acetate), whereby the title compound (0.1 g) was obtained as amorphous powder. ^{1}H NMR ($CDCl_3$) δ: 1.72-1.80 (2H, m), 2.00-2.12 (2H, m), 2.28 (6H, s), 2.40-2.50 (1H, m), 2.60-2.70 (1H, m), 2.87 (2H, t, J = 6.7 Hz), 3.04 (2H, d, J = 6.6 Hz), 4.83 (1H, t, J = 5.9 Hz), 6.70-6.75 (1H, m), 6.87 (1H, d, J = 8.4 Hz), 7.22 (1H, s), 7.37-7.52 (8H, m).

Example 5

(E)-3-[1-[(4'-Chloro[1,1-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-N,N-dimethyl-2-propen-1-amine

[0431]



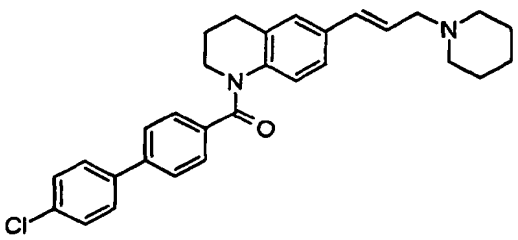
[0432] Concd. sulfuric acid (4 drops) was added to a solution of 3-[1-[(4'-chloro[1,1-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-3-hydroxy-N,N-dimethyl-1-propanamine (0.1 g) obtained in Example 4 in acetic acid (1 mL), and the mixture was stirred at 50 to 55 °C for 3 hours. After the solvent was distilled away under reduced pressure, the residues were made basic with 2 N aqueous sodium hydroxide and then extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. The resultant residues were purified by alumina column chromatography (developing solvent; ethyl acetate) and crystallized from diethyl ether, whereby the title compound (75 mg) was obtained as colorless powder with a mp of 162 to 164 °C.
^{1}H NMR ($CDCl_3$) δ: 2.02-2.13 (2H, m), 2.26 (6H, s), 2.85 (2H, t, J = 6.6 Hz), 3.04 (2H, d, J = 6.4 Hz), 3.93 (2H, t, J = 6.4 Hz), 6.16 (1H, dt, J = 6.4, 15.9 Hz), 6.40 (1H, d, J = 15.9 Hz), 6.68 (1H, d, J = 8.5 Hz), 6.91 (1H, d, J = 8.5 Hz), 7.19 (1H, s), 7.37-7.53 (8H, m).

Elemental analysis for $C_{27}H_{27}ClN_2O$			
Calcd.	C, 75.25;	H, 6.31;	N, 6.50.
Found	C, 74.90;	H, 6.52;	N, 6.35.

Example 6

1-[(4'-Chloro[1,1-biphenyl]-4-yl)carbonyl]-6-[(E)-3-piperidino-1-propenyl]-1,2,3,4-tetrahydroquinoline

[0433]



[0434] Using (E)-1-[1-[(4'-chloro[1,1'-biphenyl]-4-yl) carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-3-piperidino-2-pro-

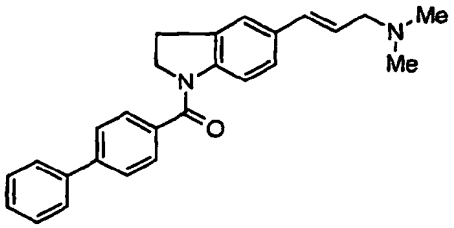
pen-1-one obtained in Reference Example 11, the title compound was obtained as colorless crystals with a mp of 141 to 143 °C by the same procedures as in Examples 4 and 5. ^{1}H NMR ($CDCl_3$) δ: 1.42-1.65 (6H, m), 2.00-2.09 (2H, m), 2.35-2.48 (4H, m), 2.84 (2H, t, J = 6.4 Hz), 3.08 (2H, d, J = 6.7 Hz), 3.92 (2H, t, J = 6.4 Hz), 6.20 (1H, dt, J = 6.7, 15.6 Hz), 6.38 (1H, d, J = 15.6 Hz), 6.66 (1H, d, J = 8.5 Hz), 6.89 (1H, d, J = 8.5 Hz), 7.18 (1H, s), 7.38-7.52 (8H, m).

Elemental analysis for $C_{30}H_{31}ClN_2O$			
Calcd.	C, 76.50;	H, 6.63;	N, 5.95.
Found	C, 76.40;	H, 6.64;	N, 5.65.

Example 7

(E)-3-[1-[([1,1'-Biphenyl]-4-yl)carbonyl]-2,3-dihydro-1H-indol-5-yl]-N,N-dimethyl-2-propen-1-amine

[0435]



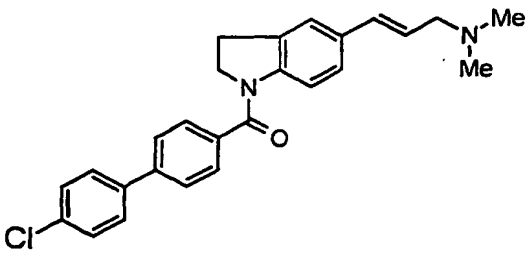
[0436] Using (E)-3-[2,3-dihydro-1H-indol-5-yl]-N,N-dimethyl-2-propen-1-amine obtained in Reference Example 13, the title compound was obtained as colorless crystals with a mp of 174 to 176 °C by the same procedure as in Example 2. ^{1}H NMR ($CDCl_3$) δ: 2.27 (6H, s), 3.06 (2H, d, J = 6.0 Hz), 3.13 (2H, t, J = 8.1 Hz), 4.15 (2H, br), 6.11-6.23 (1H,m), 6.46 (1H, d, J = 15.9 Hz), 7.06-7.28 (2H, m), 7.36-7.51 (3H, m), 7.61-7.70 (7H, m).

Elemental analysis for $C_{26}H_{26}N_2O$			
Calcd.	C, 81.64;	H, 6.85;	N, 7.32.
Found	C, 81.31;	H, 6.84;	N, 7.29.

Example 8

(E)-3-[1-[(4'-Chloro[1,1'-biphenyl]-4-yl)carbonyl]-2,3-dihydro-1H-indol-5-yl]-N,N-dimethyl-2-propen-1-amine

[0437]

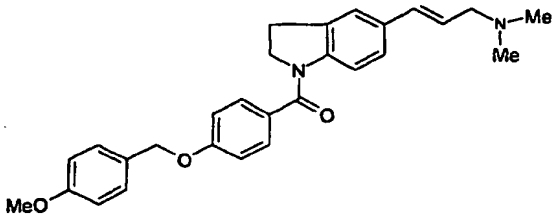


[0438] Using (E)-3-[2,3-dihydro-1H-indol-5-yl]-N,N-dimethyl-2-propen-1-amine obtained in Reference Example 13, the title compound was obtained as colorless crystals with a mp of 208 to 211 °C by the same procedure as in Example 2. ^{1}H NMR ($CDCl_3$) δ: 2.27 (6H, s), 3.06 (2H, d, J = 6.6 Hz), 3.12 (2H, t, J = 8.2 Hz), 4.14 (2H, br), 6.12-6.23 (1H,m), 6.46 (1H, d, J = 15.3 Hz), 7.06-7.28 (2H, m), 7.44 (2H, d, J = 6.6 Hz), 7.56 (2H, d, J = 6.6 Hz), 7.63 (5H, s).

Example 9

(E)-3-[1-[4-[(4-Methoxybenzyl)oxy]benzoyl]-2,3-dihydro-1H-indol-5-yl]-N,N-dimethyl-2-propen-1-amine

[0439]



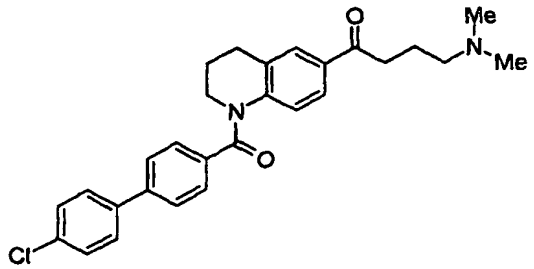
[0440] Using (E)-3-[2,3-dihydro-1H-indol-5-yl]-N,N-dimethyl-2-propen-1-amine obtained in Reference Example 13, the title compound was obtained as colorless crystals with a mp of 164 to 166 °C by the same procedure as in Example 2.
^{1}H NMR ($CDCl_3$) δ: 2.27 (6H, s), 3.04-3.12 (4H, m), 3.83 (3H, s), 4.12 (2H, t, J = 8.2 Hz), 5.04 (2H, s), 6.10-6.21 (1H, m), 6.45 (1H, d, J = 15.9 Hz), 6.90-7.30 (7H, m), 7.37 (2H, d, J = 8.7 Hz), 7.54 (2H, d, J = 8.4 Hz).

Elemental analysis for $C_{28}H_{30}N_2O_3$			
Calcd.	C, 75.99;	H, 6.83;	N, 6.33.
Found	C, 75.77;	H, 6.86;	N, 6.21.

Example 10

1-[1-[(4'-Chloro[1,1'-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-4-(dimethylamino)-1-butanone

[0441]

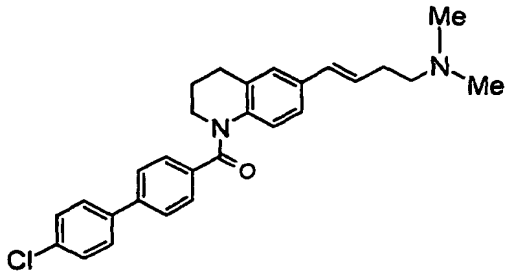


[0442] Using 1-(1,2,3,4-tetrahydro-6-quinolinyl)-4-(dimethylamino)-1-butanone obtained in Reference Example 14, the title compound was obtained as oily matter by the same procedure as in Reference Example 5.
^{1}H NMR ($CDCl_3$) δ: 1.84-1.96 (2H, m), 2.04-2.13 (2H, m), 2.21 (6H, s), 2.33 (2H, t, J = 7.1 Hz), 2.90-3.20 (4H, m), 3.95 (2H, t, J = 6.4 Hz), 6.85 (1H, d, J = 8.6 Hz), 7.38-7.62 (9H, m), 7.82 (1H, s).

Example 11

(E)-4-[1-[(4'-Chloro[1,1'-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-N,N-dimethyl-3-buten-1-amine

[0443]

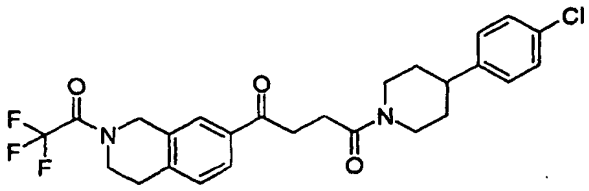


[0444] Using 1-[1-[(4'-chloro[1,1'-biphenyl]-4-yl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-4-(dimethylamino)-1-butanone obtained in Example 10, the title compound was obtained as colorless crystals with a mp of 142 to 144 °C by the same procedures as in Examples 4 and 5.
^{1}H NMR ($CDCl_3$) δ: 2.01-2.11 (2H, m), 2.25 (6H, s), 2.28-2.43 (4H, m), 2.84 (2H, t, J = 6.6 Hz), 3.92 (2H, t, J = 6.4 Hz), 6.06-6.18 (1H, m), 6.32 (1H, d, J = 15.6 Hz), 6.63 (1H, brd, J = 8.1 Hz), 6.86 (1H, d, J = 8.4 Hz), 7.15 (1H, s), 7.37-7.52 (8H, m).

Example 12

4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-[2-(trifluoroacetyl)-1,2,3,4-tetrahydro-7-isoquinolinyl]-1-butanone

[0445]

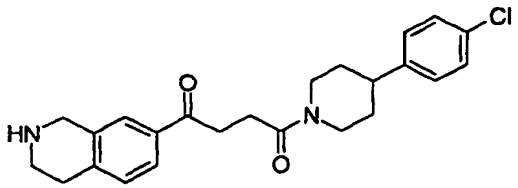


[0446] A solution of 4-oxo-4-[2-(trifluoroacetyl)-1,2,3,4-tetrahydro-7-isoquinolinyl]butanoic acid (1.0 g, 3.04 mmol) obtained in Reference Example 15, 4-chlorophenyl piperidine hydrochloride (708 mg, 3.05 mmol) and triethylamine (0.85 ml, 6.1 mmol) in dimethylformamide (8 ml) was stirred at room temperature for 20 minutes and then cooled to 0 °C. Diethyl cyanophosphate (0.463 ml, 3.05 mmol) was added to the reaction mixture, stirred at 0 °C for 30 minutes, poured into water and extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure and purified by silica gel column chromatography (developing solvent; ethyl acetate), whereby 1.1 g of the title compound was obtained as colorless crystals.
^{1}H-NMR ($CDCl_3$) δ: 1.57 (2H, m) , 1.90 (2H, m), 2.68 (2H, m) , 2.85 (2H, m), 3.00 (2H, m), 3.13 (1H, m), 3.33 (2H, m), 3.88 (2H, m), 4.13 (1H, m), 4.74 (1H, m), 4.81 (2H, m), 7.31-7.12 (5H, m), 7.93-7.79 (2H, m).
Melting point: 142 °C (dec.) (crystallizing solvent: ethanol-diisopropyl ether).

Example 13

4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-(1,2,3,4-tetrahydro-7-isoquinolinyl]-1-butanone

[0447]

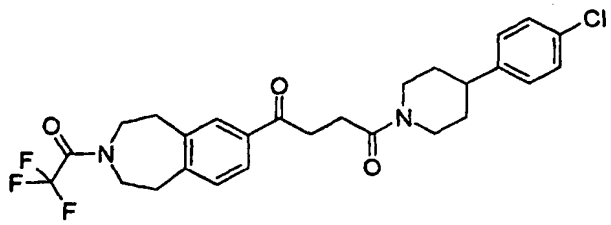


[0448] A solution of 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-[2-(trifluoroacetyl)-1,2,3,4-tetrahydro-7-isoquinolinyl]-1-butanone (1.1 g, 2.17 mmol) and potassium carbonate (900 mg, 6.5 mmol) in a mixed solvent of water (10 ml) and methanol (40 ml) was stirred at room temperature for 2 hours and then extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, whereby 810 mg of the title compound was obtained as colorless powder.
^{1}H-NMR ($CDCl_3$) δ: 1.60 (2H, m), 1.89 (2H, m), 2.91-2.61 (6H, m), 3.19 (2H, m) , 3.33 (2H, t, J = 6.6 Hz), 3.70 (2H, q, J = 6.9 Hz), 4.10 (2H, s), 4.14 (1H, d, J = 13.2 Hz), 4.75 (1H, d, J = 13.2 Hz), 7.28-7.12 (5H, m), 7.70 (1H, s), 7.80 (1H, d, J = 8.1 Hz).
Melting point: 121-122 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 14

4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone

[0449]



[0450] Using 4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl]butanoic acid obtained in Reference Example 16, the title compound was obtained as colorless powder by the same procedure as in Example 12.
^{1}H-NMR ($CDCl_3$) δ: 1.45-2.00 (4H, m), 2.55-2.90 (4H, m), 2.97-3.28 (5H, m), 3.34 (2H, t, J=6.4Hz), 3.64-3.84 (4H, m), 4.04-4.21 (1H, m), 4.68-4.84 (1H, m), 7.14 (2H, d, J=8.4Hz), 7.20-7.34 (3H, m), 7.80-7.90 (2H, m).

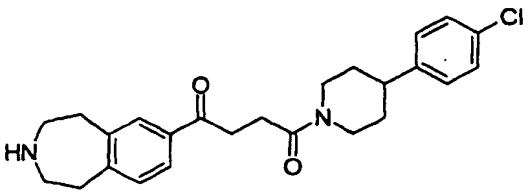
Elemental analysis for $C_{27}H_{28}ClF_3N_2O_3$			
Calcd.	C, 62.25;	H, 5.42;	N, 5.38.
Found	C, 62.23;	H, 5.44;	N, 5.29.

Melting point: 131-132 °C (crystallizing solvent: isopropanol-diisopropyl ether)

Example 15

4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone

[0451]



[0452] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone obtained in Example 14, the title compound was obtained as colorless powder by the same procedure as in Example 13.
^{1}H-NMR ($CDCl_3$) δ: 1.47-2.00 (4H, m), 2.57-2.88 (5H, m), 2.98 (8H, br), 3.07-3.27 (1H, m), 3.50 (2H, t, J=6.6Hz), 4.05-4.21 (1H, m), 4.72-4.84 (1H, m), 7.10-7.34 (5H, m), 7.74-7.83 (2H, m).

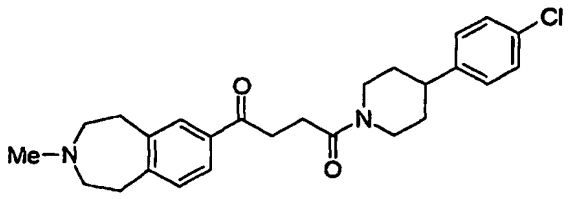
Elemental analysis for $C_{25}H_{29}ClN_2O_2$			
Calcd.	C, 70.66;	H, 6.88;	N, 6.59.
Found	C, 70.22;	H, 7.13;	N, 6.51.

Melting point: 148-149 °C (crystallizing solvent: ethanol)

Example 16

4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone

[0453]



[0454] A mixture of 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone (0.3 g, 0.70 mmol) obtained in Example 15, formaldehyde (0.086 ml, 1.06 mmol) and formic acid (0.9 ml) was heated at 100 °C for 4 hours, then poured into water, made basic with 8 N aqueous sodium hydroxide and extracted with ethyl acetate. The extract was washed with water and then with a saturated saline solution, and dried over anhydrous magnesium sulfate. After the solvent was distilled away under reduced pressure, the residues were purified by alumina column chromatography (developing solvent; ethyl acetate-methanol = 10 : 1), whereby 0.15 g of the title compound was obtained as colorless powder.
^{1}H-NMR ($CDCl_3$) δ: 1.47-2.00 (4H, m), 2.38 (3H, s), 2.47-2.88 (8H, m), 2.95-3.06 (4H, m), 3.08-3.28 (1H, m), 3.35 (2H, t, J=6.8Hz), 4.07-4.21 (1H, m), 4.71-4.86 (1H, m), 7.08-7.34 (5H, m), 7.75-7.85 (2H, m).

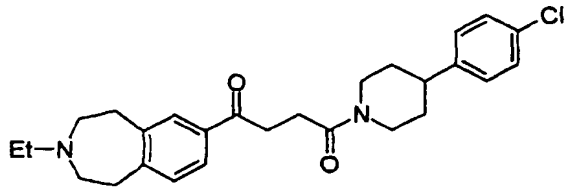
Elemental analysis for $C_{26}H_{31}ClN_2O_2$			
Calcd.	C, 71.14;	H, 7.12;	N, 6.38.
Found	C, 70.92;	H, 7.35;	N, 6.41.

Melting point: 143-145 °C (crystallizing solvent: ethyl acetate-diethyl ether)

Example 17

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(3-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-1-butanone

[0455]



[0456] A solution of 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone (200 mg, 0.47 mmol) obtained in Example 15, iodoethane (0.0376 ml, 0.47 mmol) and potassium carbonate (138 mg, 1.0 mmol) in acetonitrile (5 ml) was stirred at room temperature for 12 hours, then poured into water and extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, and the residues were purified by alumina silica gel column chromatography (developing solvent; ethyl acetate), whereby 101 mg of the title compound was obtained as colorless powder.

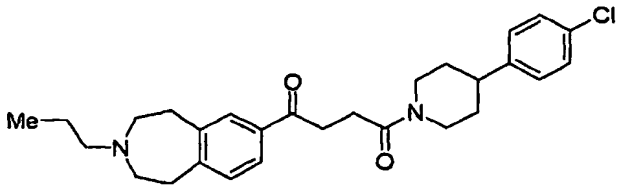
^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J = 7.0 Hz), 1.62 (2H, m), 1.94 (2H, m), 2.72-2.52 (8H, m), 2.79 (2H, t, J = 6.4 Hz), 2.97 (4H, m), 3.23 (1H, m), 3.35 (2H, t, J = 6.6 Hz), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.35-7.11 (5H, m), 7.79 (2H, m).

Melting point: 156-157 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 18

4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-(3-propyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone

[0457]



[0458] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17.

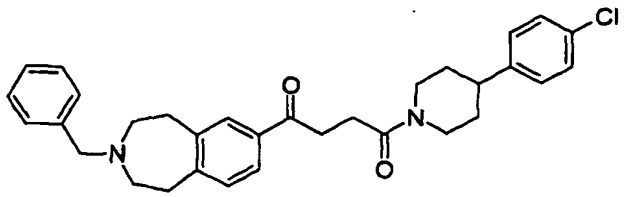
^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J = 7.2 Hz), 1.62 (4H, m) , 1.89 (2H, m), 2.45 (2H, t, J = 8.0 Hz), 2.72-2.66 (6H, m), 2.79 (2H, t, J = 6.4 Hz), 2.97 (4H, m), 3.23 (1H, m), 3.35 (2H, t, J = 6.6 Hz), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.35-7.11 (5H, m), 7.79 (2H, m).

Melting point: 151-152 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 19

1-(3-Benzyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-butanone

[0459]

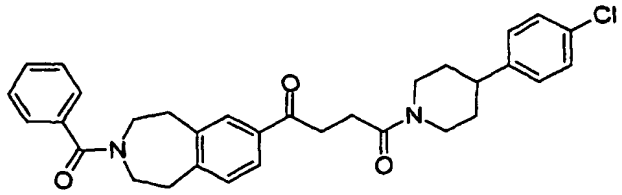


[0460] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (2H, m), 1.89 (2H, m), 2.72-2.65 (6H, m) , 2.85 (2H, t, J = 6.4 Hz), 2.97 (4H, m) , 3.23 (1H, m), 3.34 (2H, t, J = 6.6 Hz), 3.64 (2H, s), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.35-7.11 (10H, m), 7.79 (2H, m).
Melting point: 133-134 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 20

1-(3-Benzoyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-butanone

[0461]

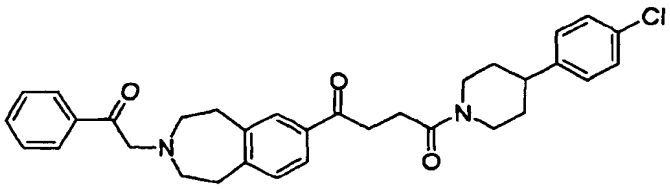


[0462] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (2H, m) , 1.89 (2H, m) , 3.17-2.59 (9H, m), 3.34 (2H, t, J = 6.6 Hz), 3.53 (2H, m), 3.87 (2H, m), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.35-7.11 (10H, m), 7.79 (2H, m).
Melting point: 158-160 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 21

4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-[3-(2-oxo-2-phenylethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone

[0463]

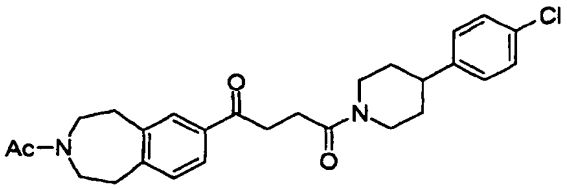


[0464] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (2H, m), 1.89 (2H, m), 2.86-2.58 (8H, m) , 3.03 (4H, m) , 3.17 (1H, m) , 3.35 (2H, t, J = 6.6 Hz), 3.96 (2H, s), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.31-7.11 (5H, m), 7.55-7.43 (3H, m), 7.79 (2H, m), 8.05 (2H, m).
Melting point: 108-109 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 22

1-(3-Acetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-butanone

[0465]

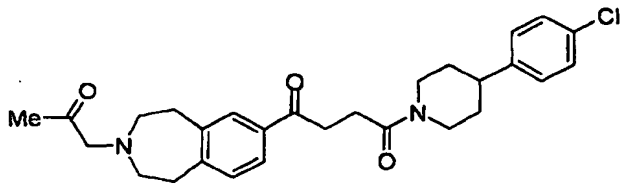


[0466] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (2H, m), 1.89 (2H, m), 2.66 (3H, s), 2.58 (4H, m), 2.87 (2H, t, J = 6.6 Hz), 3.11 (4H, m), 3.17 (1H, m), 3.34 (2H, t, J = 6.6 Hz), 3.76-3.58 (4H, m), 4.13 (1H, d, J = 15.6 Hz), 4.73 (1H, d, J = 12 Hz), 7.31-7.11 (5H, m), 7.81 (2H, m).
Melting point: 110-112 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 23

4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-[3-(2-oxopropyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone

[0467]

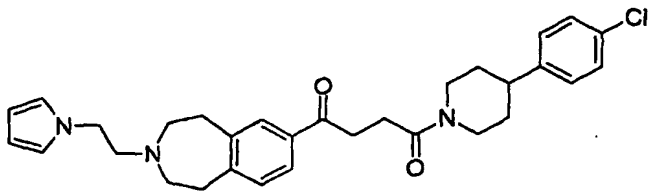


[0468] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (2H, m), 1.89 (2H, m), 2.22 (3H, s), 2.67 (4H, m), 2.87 (2H, t, J = 6.6 Hz), 3.00 (4H, m), 3.17 (1H, m), 3.78-3.32 (4H, m), 4.13 (1H, d, J = 15.6 Hz), 4.73 (1H, d, J = 12 Hz), 7.31-7.11 (5H, m), 7.81 (2H, m).
Melting point: 119-120 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 24

4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-[3-[2-(1H-pyrrol-1-yl)ethyl]-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone

[0469]

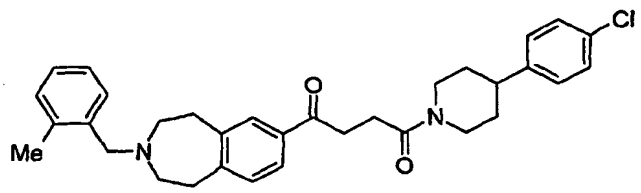


[0470] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (2H, m), 1.89 (2H, m), 2.95-2.59 (14H, m), 3.17 (1H, m), 3.34 (2H, t, J = 6.2 Hz), 4.18-4.00 (3H, m), 4.75 (1H, m), 6.15 (2H, m), 6.70 (2H, m), 7.31-7.11 (5H, m), 7.81 (2H, m).
Melting point: 96-97 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 25

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-[3-(2-methylbenzyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-4-oxo-1-butanone

[0471]

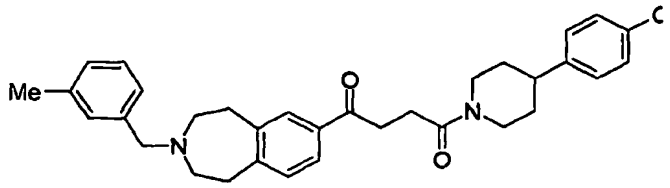


[0472] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (2H, m) , 1.89 (2H, m), 2.40 (3H, s), 2.72-2.65 (6H, m) , 2.82 (2H, t, J = 6.4 Hz), 2.94 (4H, m) , 3.23 (1H, m), 3.35 (2H, t, J = 6.6 Hz), 3.54 (2H, s), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.35-7.11 (9H, m), 7.79 (2H, m).
Melting point: 108-109 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 26

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-[3-(3-methylbenzyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-4-oxo-1-butanone

[0473]

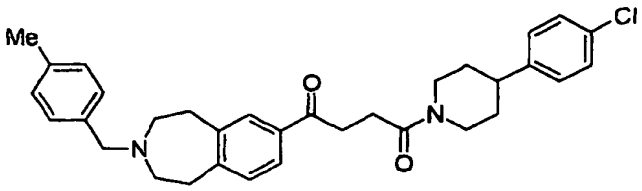


[0474] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (2H, m), 1.89 (2H, m), 2.36 (3H, s), 2.72-2.65 (6H, m), 2.82 (2H, t, J = 6.4 Hz), 2.94 (4H, m), 3.23 (1H, m), 3.35 (2H, t, J = 6.6 Hz), 3.60 (2H, s), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.35-7.11 (9H, m), 7.79 (2H, m).
Melting point: 127-128 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 27

4-[4-(4-Chlorophenyl)piperidin-1-yl]-1-[3-(4-methylbenzyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-4-oxobutan-1-one

[0475]

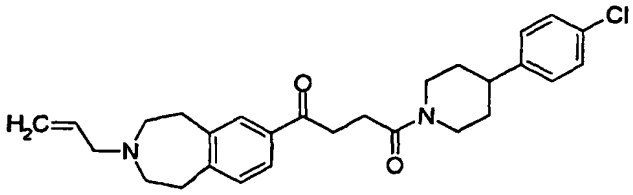


[0476] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (2H, m), 1.88 (2H, m), 2.35 (3H, s), 2.64 (6H, m) , 2.78 (2H, t, J = 6.4 Hz), 2.95 (4H, m) , 3.23 (1H, m), 3.34 (2H, t, J = 6.6 Hz), 3.60 (2H, s), 4.13 (1H, m), 4.76 (1H, m), 7.35-7.11 (9H, m), 7.79 (2H, m).
Melting point: 137-138 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 28

1-(3-Allyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl) piperidin-1-yl]-4-oxobutan-1-one

[0477]

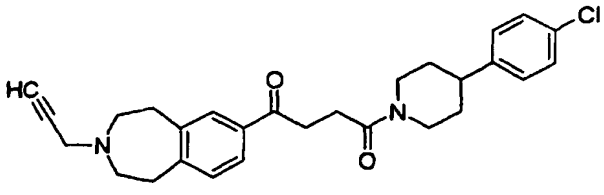


[0478] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (2H, m) , 1.88 (2H, m) , 2.65 (7H, m) , 2.78 (2H, t, J = 6.4 Hz), 2.97 (4H, m), 3.23 (2H, m), 3.35 (2H, t, J = 6.6 Hz), 4.13 (1H, m), 4.76 (1H, m), 5.23-5.15 (2H, m), 5.90 (1H, m), 7.31-7.11 (5H, m), 7.79 (2H, m).
Melting point: 136-137 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 29

4-[4-(4-Chlorophenyl)piperidin-1-yl]-4-oxo-1-(2-propynyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one

[0479]

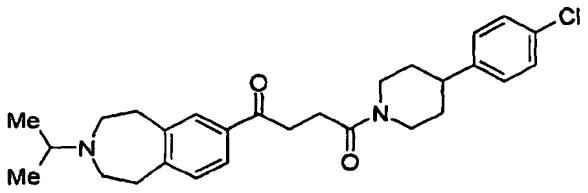


[0480] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (2H, m), 1.88 (2H, m), 2.21 (1H, s), 3.43-2.58 (15H, m), 4.13 (2H, m), 4.76 (1H, m), 5.07 (1H, m), 5.84 (1H, m), 7.31-7.11 (5H, m), 7.79 (2H, m).
Melting point: 132-134 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 30

4-[4-(4-Chlorophenyl)piperidin-1-yl]-1-(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxobutan-1-one

[0481]

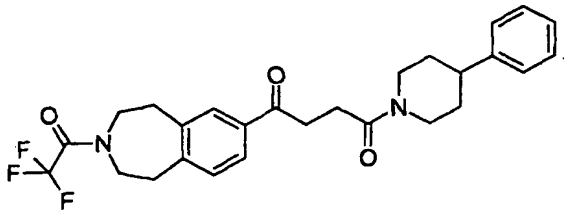


[0482] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (6H, d, J = 6.6 Hz), 1.62 (4H, m), 1.89 (2H, m), 2.64 (7H, m), 2.82 (2H, t, J = 6.4 Hz), 2.95 (4H, m), 3.23 (1H, m), 3.35 (2H, t, J = 6.6 Hz), 4.13 (1H, m), 4.76 (1H, m), 7.35-7.11 (5H, m), 7.79 (2H, m).
Melting point: 139-140 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 31

4-Oxo-4-(phenyl-1-piperidinyl)-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone

[0483]



[0484] Using 4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanoic acid obtained in Reference Example 16, the title compound was obtained as colorless powder by the same procedure as in Example 12. ^{1}H-NMR ($CDCl_3$) δ: 1.48-1.78 (2H, m), 1.82-2.00 (2H, m), 2.60-2.88 (4H, m), 2.98-3.10 (4H, m), 3.13-3.26 (1H, m), 3.34 (2H, t, J=6.5Hz), 3.67-3.83 (4H, m), 4.07-4.18 (1H, m), 4.72-4.82 (1H, m), 7.16-7.37 (6H, m), 7.80-7.90 (2H, m).

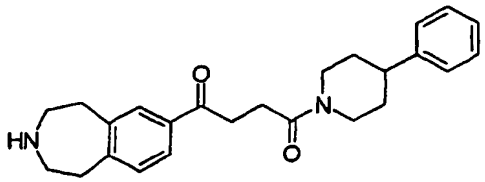
Elemental analysis for $C_{27}H_{29}F_3N_2O_3$			
Calcd.	C, 66.65;	H, 6.01;	N, 5.76.
Found	C, 66.45;	H, 6.09;	N, 5.56.

Melting point: 132-133 °C (crystallizing solvent: isopropanol).

Example 32

4-Oxo-4-(phenyl-1-piperidinyl)-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone

[0485]



[0486] Using 4-oxo-4-(phenyl-1-piperidinyl)-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone obtained in Example 31, the title compound was obtained as colorless powder by the same procedure as in Example 13.

^{1}H-NMR ($CDCl_3$) δ: 1.54-2.00 (5H, m), 2.60-2.87 (4H, m), 2.97 (8H, br), 3.12-3.24 (1H, m), 3.35 (2H, t, J=6.7Hz), 4.08-4.20 (1H, m), 4.73-4.83 (1H, m), 7.16-7.37 (6H, m), 7.77-7.82 (2H, m).

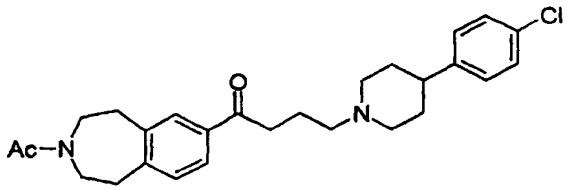
Elemental analysis for $C_{25}H_{30}N_2O_2$			
Calcd.	C, 76.89;	H, 7.74;	N, 7.17.
Found	C, 76.44;	H, 7.68;	N, 7.02.

Melting point: 114 °C (crystallizing solvent: isopropanol-diisopropyl ether).

Example 33

4-(3-Acetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(chlorophenyl)-1-piperidinyl]-1-butanone

[0487]



1) Aluminum chloride (2.9 g, 21.7 mmol) was added little by little to a mixture of 3-acetyl-2,3,4,5-tetrahydro-1H-3-benzazepine (2 g, 10.5 mmol) and 4-chlorobutyryl chloride (1.56 g, 11 mmol) in nitromethane (5 ml) at room temperature and stirred for 2 hours at room temperature. The reaction solution was poured into ice water which was then extracted with ethyl acetate, washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, whereby 1-(3-acetyl-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl)-4-chloro-1-butanone (2.9 g) was obtained.

2) A mixture of 1-(3-acetyl-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl)-4-chloro-1-butanone (0.75 g, 2.55 mmol) obtained in 1) above, 4-chlorophenyl piperidine (5.1 g, 5.1 mmol) and potassium iodide (0.05 g) in toluene (15 ml) was heated under reflux for 16 hours. The reaction solution was poured into water, made basic with 1 N aqueous sodium hydroxide and extracted with ethyl acetate. The extract was washed with a saturated saline solution and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, and the residues were purified by silica gel column chromatography (developing solvent; ethyl acetate : methanol = 1 : 1), whereby 0.6 g of the title compound was obtained as colorless powder.

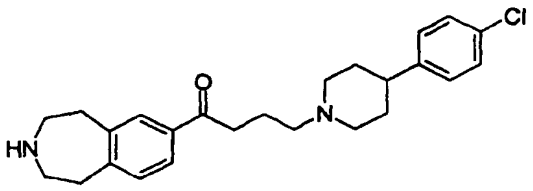
^{1}H-NMR ($CDCl_3$) δ: 1.54-2.25 (11H, m), 2.37-2.56 (3H, m), 2.90-3.12 (8H, m), 3.53-3.64 (2H, m), 3.66-3.79 (2H, m),

7.07-7.31 (5H, m), 7.72-7.82 (2H, m).
Melting point: 131-132 °C (crystallizing solvent: isopropanol-diisopropyl ether).

Example 34

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(2,3;4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone

[0488]



[0489] Using 1-(3-acetyl-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-1-butanone obtained in Example 33, the title compound was obtained as colorless powder by the same procedure as in Reference Example 10.
^{1}H-NMR ($CDCl_3$, free base) δ: 1.53-2.13 (9H, m), 2.35-2.55 (3H, m), 2.90-3.10 (12H, m), 7.07-7.30 (5H, m), 7.68-7.80 (2H, m).

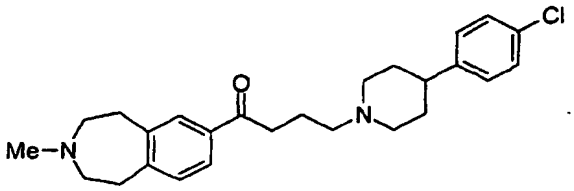
Elemental analysis for $C_{25}H_{31}ClN_2O \cdot 2HCl$			
Calcd.	C, 62.05;	H, 6.87;	N, 5.79.
Found	C, 61.93;	H, 6.78;	N, 5.48.

Melting point: 243-247 °C (dec.) (crystallizing solvent: isopropanol-diisopropyl ether).

Example 35

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone

[0490]



[0491] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl)-1-butanone obtained in Example 34, the title compound was obtained as colorless powder by the same procedure as in Example 16.
^{1}H-NMR ($CDCl_3$, free base) δ: 1.62-2.20 (8H, m), 2.36-2.67 (10H, m), 2.93-3.15 (8H, m), 7.07-7.30 (5H, m), 7.70-7.80 (2H ,m) .

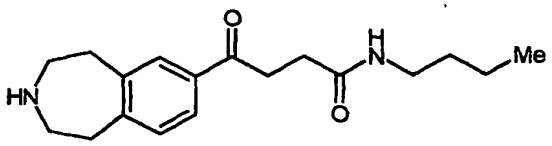
Elemental analysis for $C_{26}H_{33}ClN_2O \cdot 2HCl \cdot 0.5H_2O$			
Calcd.	C, 61.60;	H, 7.16;	N, 5.53.
Found	C, 61.73;	H, 7.32;	N, 5.48.

Melting point: 248-252 °C (dec.) (crystallizing solvent: isopropanol).

Example 36

N-Butyl-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl) butanamide trifluoroacetate

[0492]

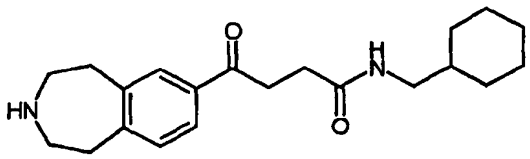


[0493] 4-Oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl] butanoic acid (30.2 mg, 0.088 mmol) obtained in Reference Example 16, n-butylamine (5.9 mg, 0.08 mol) and carbodiimide resin (136 mg, 0.12 mmol, 0.88 mmol/g) were stirred in dichloromethane (1 ml) at room temperature for 12 hours. The reaction mixture was filtered, the filtrate was concentrated, and an aqueous solution (0.5 ml) of methanol (500 µl) and potassium carbonate (331 mg, 2.4 mmol) was added to the reaction mixture and then stirred at room temperature for 12 hours. The solvent was distilled away, and the residues were purified by preparative liquid chromatography (developing solvent: 0.1 % aqueous trifluoroacetic acid/0.1 % trifluoroacetic acid in acetonitrile = 90/10 to 10/90), whereby 10.2 mg of the title compound was obtained as colorless powder.
MS (ESI) (M+1) : 303

Example 37

N-(Cyclohexylmethyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0494]

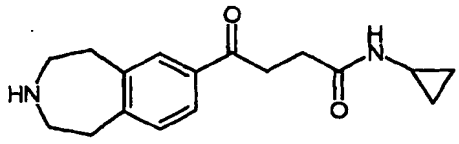


[0495] The title compound was obtained in the same manner as in Example 36.
MS(ESI)(M+1): 343

Example 38

N-Cyclohexyl-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0496]

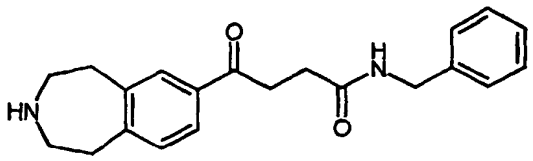


[0497] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 287

Example 39

N-Benzyl-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0498]

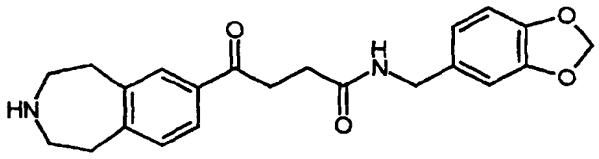


[0499] The title compound was obtained in the same manner as in Example 36.
MS(ESI) (M+1): 337

Example 40

N-(1,3-Benzodioxol-5-ylmethyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0500]

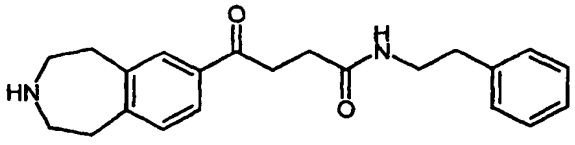


[0501] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 381

Example 41

4-Oxo-N-(2-phenetyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0502]

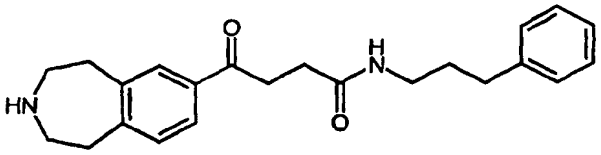


[0503] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 351

Example 42

4-Oxo-N-(3-phenylpropyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0504]

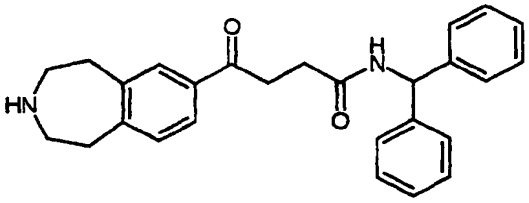


[0505] The title compound was obtained in the same manner as in Example 36.
MS(ESI)(M+1): 365

Example 43

N-Benzhydryl-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0506]

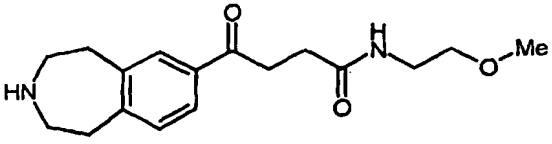


[0507] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 413

Example 44

N-(2-Methoxyethyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0508]

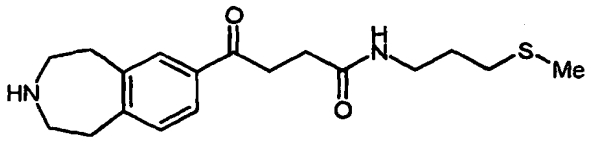


[0509] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 305

Example 45

N-[3-(Methylthio)propyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0510]

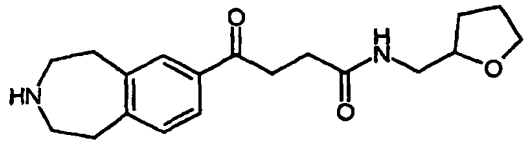


[0511] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1): 335

Example 46

4-Oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-(tetrahydrofuran-2-ylmethyl)butanamide trifluoroacetate

[0512]

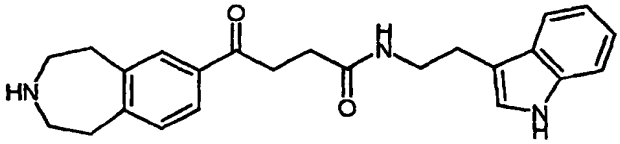


[0513] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1): 331

Example 47

N-[2-(1H-Indol-3-yl)ethyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0514]

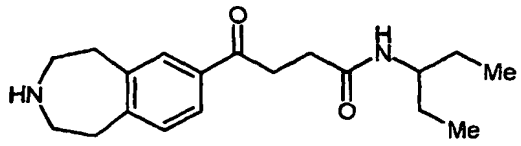


[0515] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 390

Example 48

N-(1-Ethylpropyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0516]

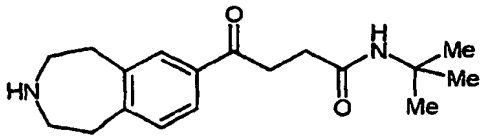


[0517] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 317

Example 49

N-(tert-Butyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0518]

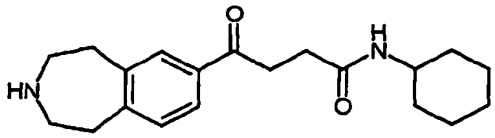


[0519] The title compound was obtained in the same manner as in Example 36.
MS(ESI)(M+1): 303

Example 50

N-(Cyclohexyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0520]

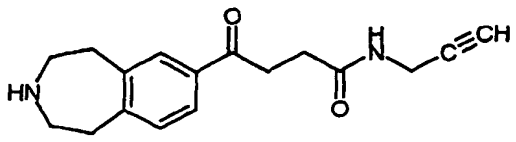


[0521] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 329

Example 51

4-Oxo-N-prop-2-ynyl-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0522]

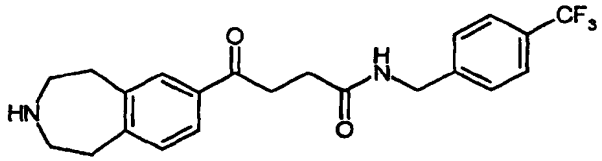


[0523] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 285

Example 52

4-Oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-[4-(trifluoromethyl)benzyl]butanamide trifluoroacetate

[0524]

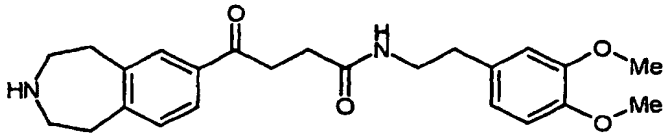


[0525] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 405

Example 53

N-[2-(3,4-Dimethoxyphenyl)ethyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0526]

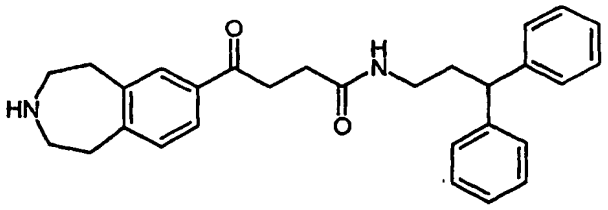


[0527] The title compound was obtained in the same manner as in Example 36.
MS(ESI)(M+1): 411

Example 54

N-(3,3-Diphenylpropyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0528]

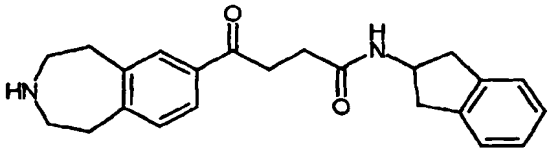


[0529] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1): 441

Example 55

N-(2,3-Dihydro-1H-inden-2-yl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0530]

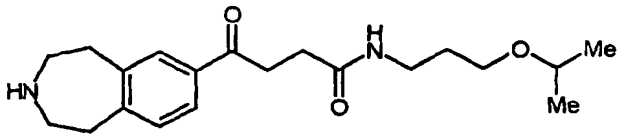


[0531] The title compound was obtained in the same manner as in Example 36.
MS(ESI)(M+1): 363

Example 56

N-(3-Isopropoxypropyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0532]

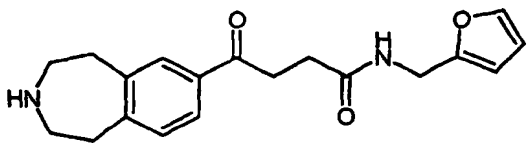


[0533] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 347

Example 57

N-(3-Furylmethyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0534]

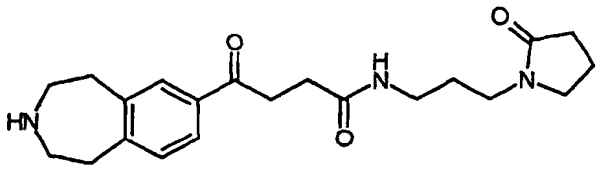


[0535] The title compound was obtained in the same manner as in Example 36.
MS(ESI)(M+1): 327

Example 58

4-Oxo-N-[3-(2-oxopyrrolidin-1-yl)propyl]-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0536]

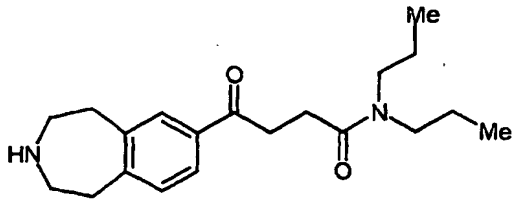


[0537] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 372

Example 59

4-Oxo-N,N-dipropyl-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0538]

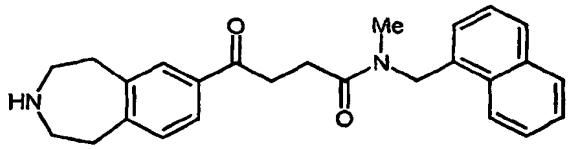


[0539] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1): 331

Example 60

N-Methyl-N-(1-naphthylmethyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0540]

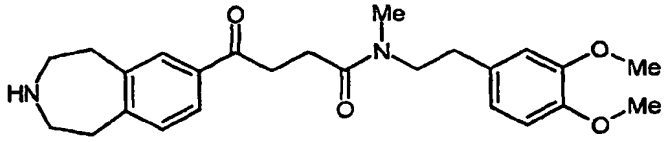


[0541] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 401

Example 61

N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0542]

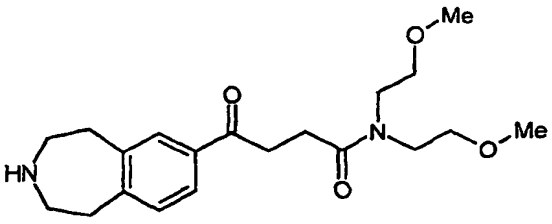


[0543] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 425

Example 62

N,N-bis(2-Methoxyethyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0544]

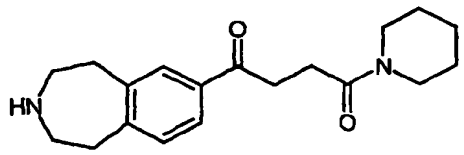


[0545] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 363

Example 63

4-Oxo-4-piperidin-1-yl-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0546]

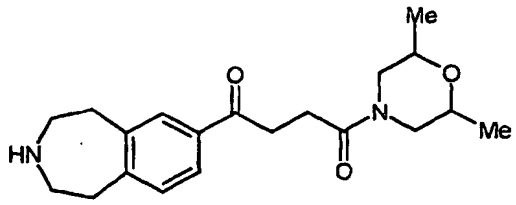


[0547] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 315

Example 64

4-(2,6-Dimethylmorpholin-4-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0548]

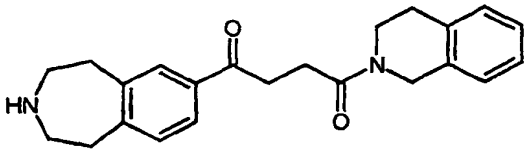


[0549] The title compound was obtained in the same manner as in Example 36.
MS(ESI)(M+1): 345

Example 65

4-(3,4-Dihydroisoquinolin-2(1H)-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0550]

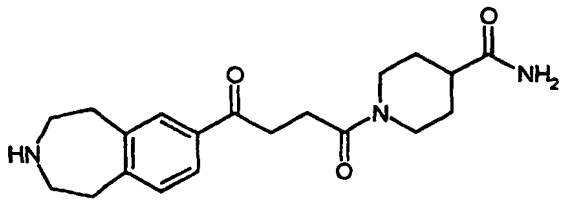


[0551] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1): 363

Example 66

1-[4-Oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanoyl]piperidine-4-carboxamide trifluoroacetate

[0552]

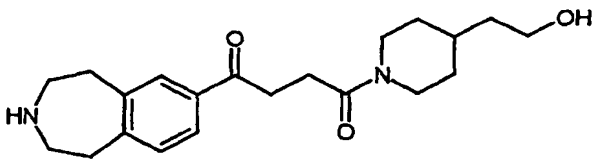


[0553] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1): 358

Example 67

4-[4-(2-Hydroxyethyl)piperidin-1-yl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0554]

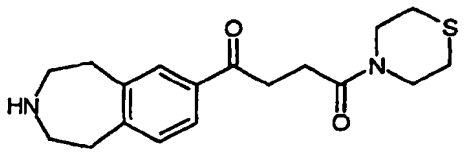


[0555] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 359

Example 68

4-Oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-thiomorphin-4-ylbutan-1-one trifluoroacetate

[0556]

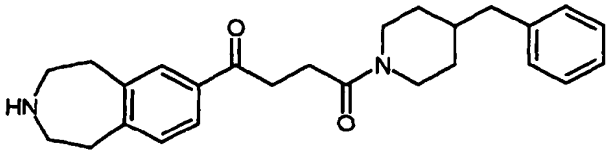


[0557] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) 333

Example 69

4-(4-Benzylpiperidin-1-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0558]

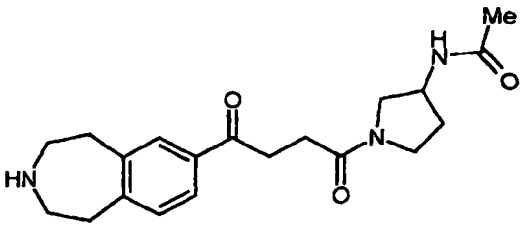


[0559] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 405

Example 70

N-[1-[4-Oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanoyl]pyrrolidin-3-yl]acetamide trifluoroacetate

[0560]

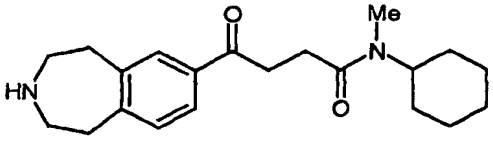


[0561] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 358

Example 71

N-Cyclohexyl-N-methyl-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0562]

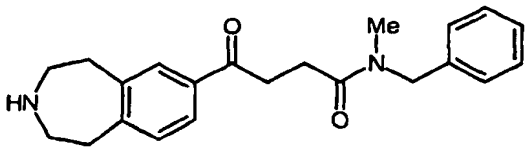


[0563] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 343

Example 72

N-Benzyl-N-methyl-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0564]

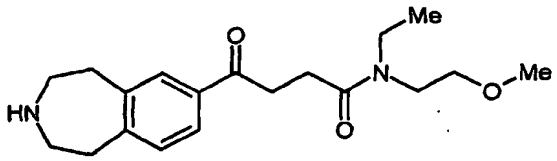


[0565] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 351

Example 73

N-Ethyl-N-(2-methoxyethyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0566]

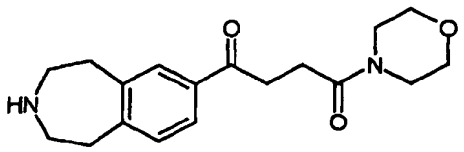


[0567] The title compound was obtained in the same manner as in Example 36.
MS(ESI) (M+1) : 333

Example 74

4-Morpholin-4-yl-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0568]

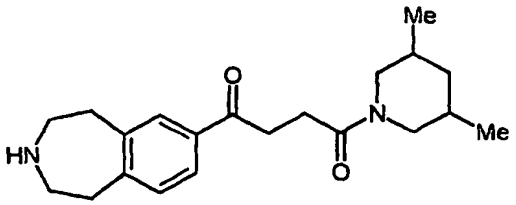


[0569] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 317

Example 75

4-(3,5-Dimethylpiperidin-1-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0570]

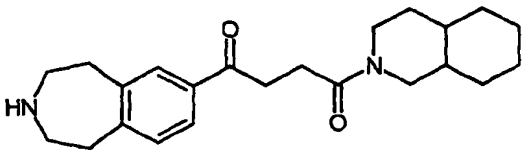


[0571] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 343

Example 76

4-Octahydroisoquinolin-2(1H)-yl-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0572]

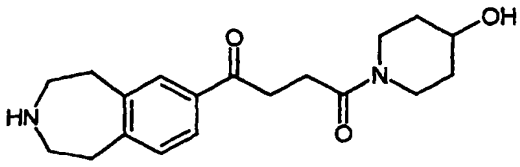


[0573] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 369

Example 77

4-(4-Hydroxypiperidin-1-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0574]

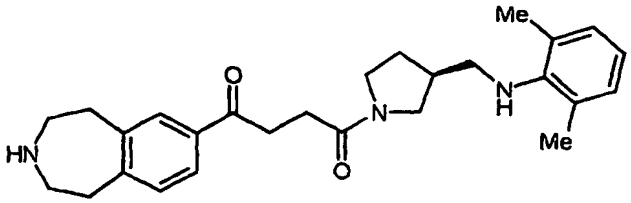


[0575] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 331

Example 78

4-((2S)-2-[[(2,6-Dimethylphenyl)amino]methyl]pyrrolidin-1-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl) butan-1-one trifluoroacetate

[0576]

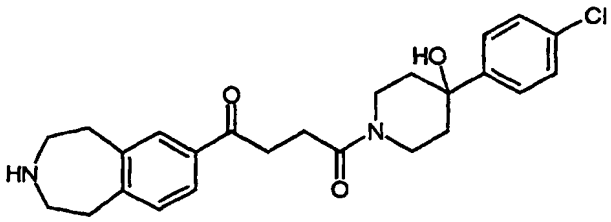


[0577] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 434

Example 79

4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0578]

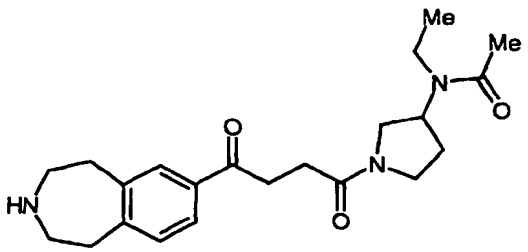


[0579] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 441

Example 80

N-Ethyl-N-[1-[4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl) butanoyl]pyrrolidin-3-yl]acetamide trifluoroacetate

[0580]



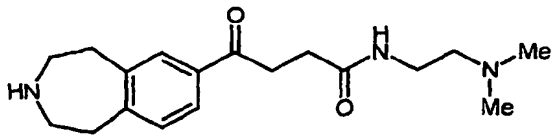
[0581] The title compound was obtained in the same manner as in Example 36.

MS (ESI) (M+1): 386

Example 81

N-[2-(Dimethylamino)ethyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0582]

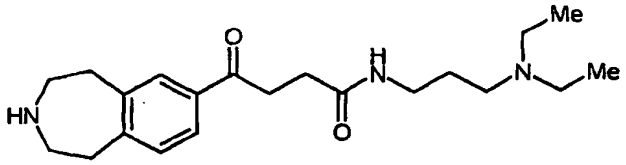


[0583] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 318

Example 82

N-[3-(Dimethylamino)propyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0584]

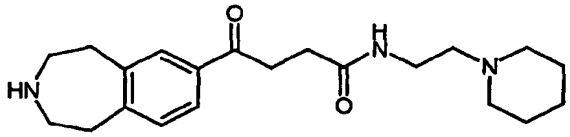


[0585] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 360

Example 83

4-Oxo-N-(2-piperidin-1-ylethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0586]

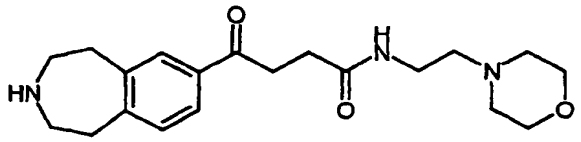


[0587] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1): 358

Example 84

N-(2-Morpholin-4-ylethyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0588]

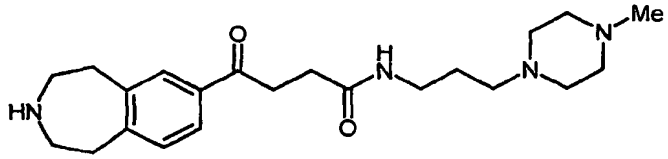


[0589] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 360

Example 85

N-[3-(4-Methylpiperazin-1-yl)propyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0590]

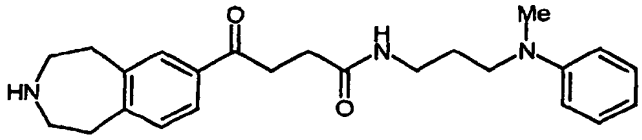


[0591] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 387

Example 86

N-[3-[Methyl(phenyl)amino]propyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0592]

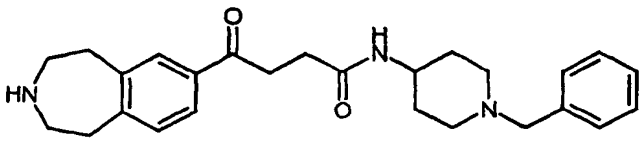


[0593] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 394

Example 87

N-(1-Benzylpiperidin-4-yl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0594]

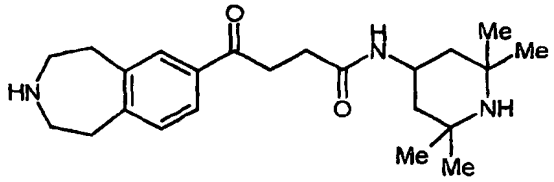


[0595] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 420

Example 88

4-Oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-(2,2,6,6-tetramethylpiperidin-4-yl)butanamide trifluoroacetate

[0596]

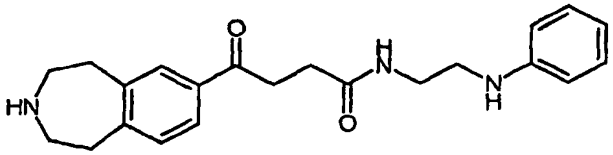


[0597] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 386

Example 89

N-(2-Anilinoethyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0598]

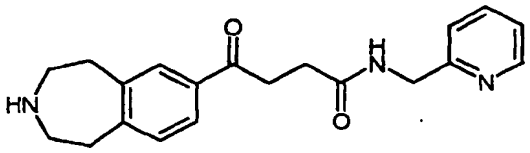


[0599] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 366

Example 90

4-Oxo-N-(pyridin-2-ylmethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0600]

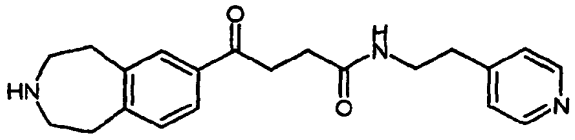


[0601] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 338

Example 91

4-Oxo-N-(pyridin-4-ylmethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0602]

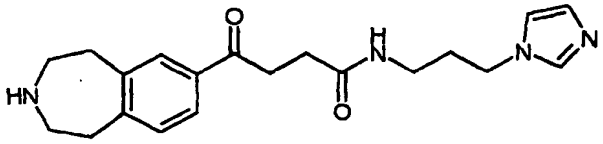


[0603] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 352

Example 92

N-[3-(1H-Imidazol-1-yl)propyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0604]

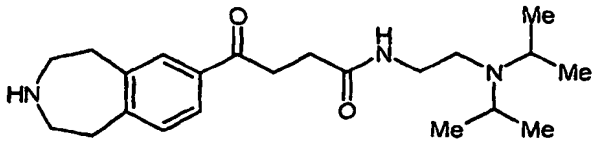


[0605] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 355

Example 93

N-[3-(Diisopropylamino)ethyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0606]

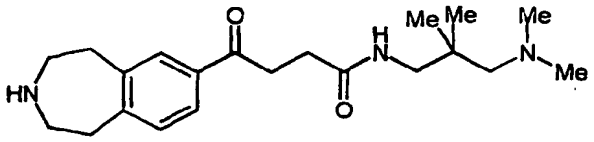


[0607] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 374

Example 94

N-[3-(Dimethylamino)-2,2-dimethylpropyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0608]

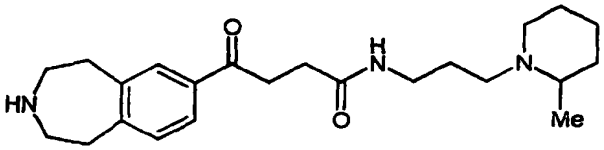


[0609] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 360

Example 95

N-[3-(2-Methylpiperidin-1-yl)propyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0610]

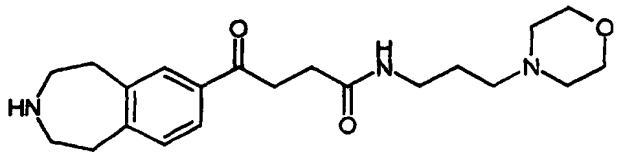


[0611] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 386

Example 96

N-(3-Morpholin-4-ylpropyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0612]

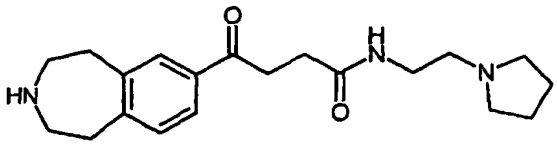


[0613] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 374

Example 97

4-Oxo-N-(2-pyrrolidin-1-ylethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0614]

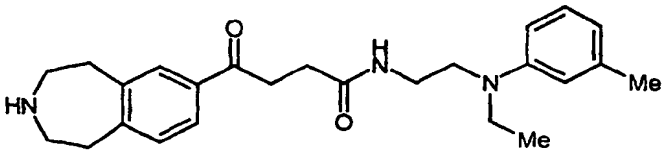


[0615] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1): 344

Example 98

N-[2-[Ethyl(2-methylphenyl)amino]ethyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0616]

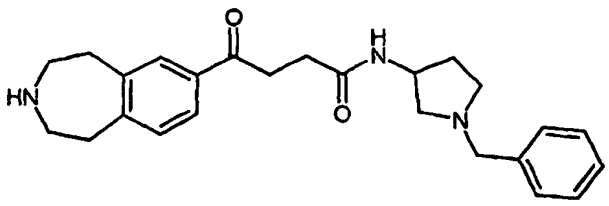


[0617] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 408

Example 99

N-(1-Benzylpyrrolidin-3-yl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0618]

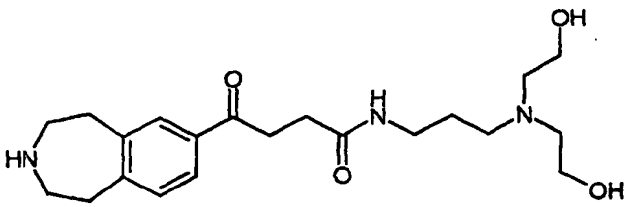


[0619] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 406

Example 100

N-[3-[bis(2-Hydroxyethyl)amino]propyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0620]

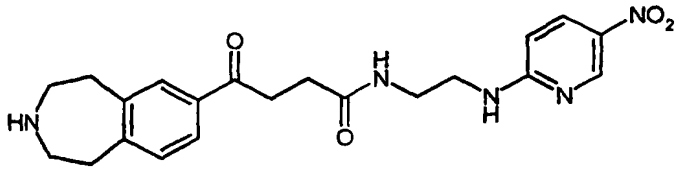


[0621] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1): 392

Example 101

N-[3-[(5-Nitropyridine)amino]ethyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0622]

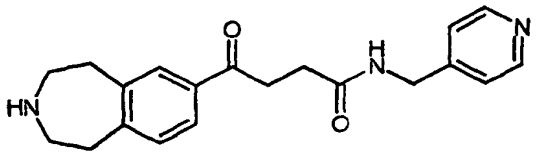


[0623] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 412

Example 102

4-Oxo-N-(pyridin-4-ylmethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0624]

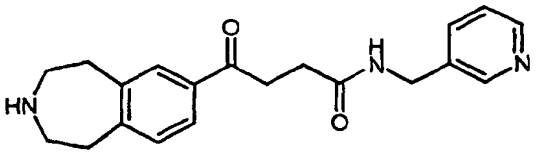


[0625] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1): 338

Example 103

4-Oxo-N-(pyridin-3-ylmethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0626]

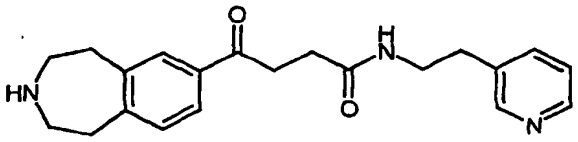


[0627] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 338

Example 104

4-Oxo-N-(2-pyridin-3-ylethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0628]

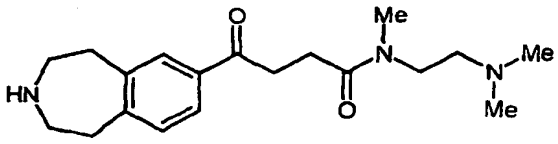


[0629] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 352

Example 105

N-[2-(Dimethylamino)ethyl]-N-methyl-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanehydrazide trifluoroacetate

[0630]

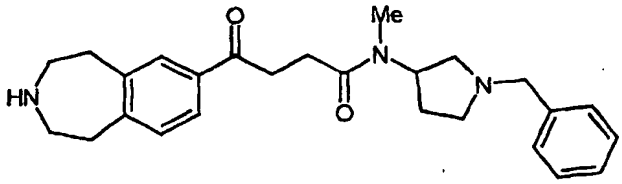


[0631] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 332

Example 106

N-(1-Benzylpyrrolidin-3-yl)-N-methyl-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0632]

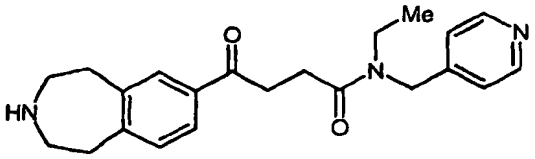


[0633] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 420

Example 107

N-Ethyl-4-oxo-N-(pyridin-4-ylmethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0634]

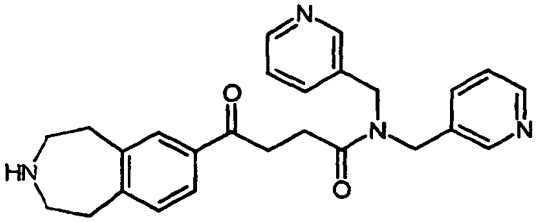


[0635] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 366

Example 108

4-Oxo-N,N-bis(pyridin-3-ylmethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0636]

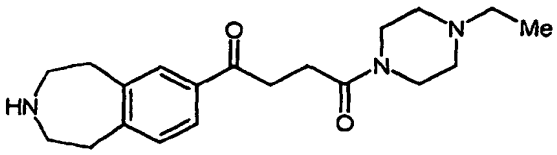


[0637] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 429

Example 109

4-(4-Ethylpiperazin-1-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0638]

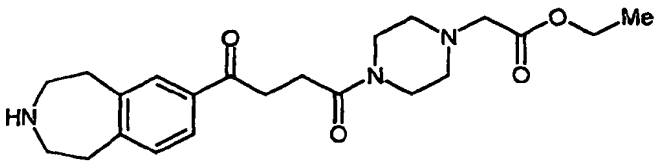


[0639] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1): 344

Example 110

Ethyl [4-[4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanoyl]piperazin-1-yl]acetate trifluoroacetate

[0640]

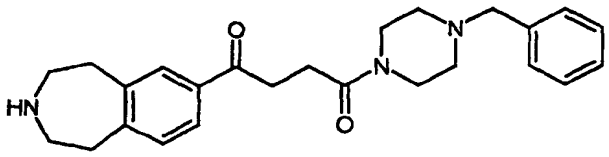


[0641] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1): 401

Example 111

4-(4-Benzylpiperazin-1-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0642]

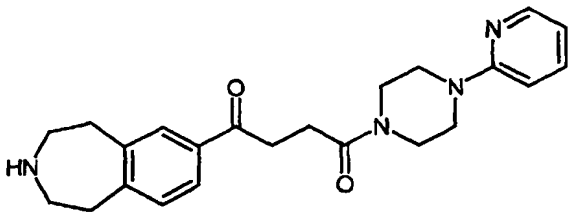


[0643] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1): 406

Example 112

4-Oxo-4-[4-(pyridin-2-yl)piperazin-1-yl]-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0644]

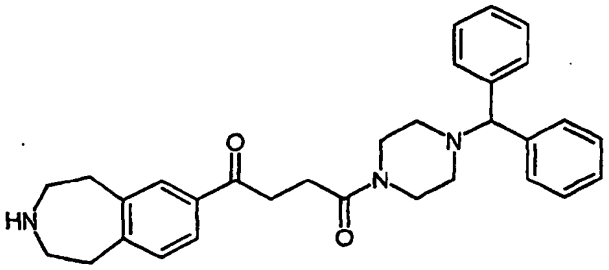


[0645] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 393

Example 113

4-(4-Benzhydrylpiperazin-1-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0646]

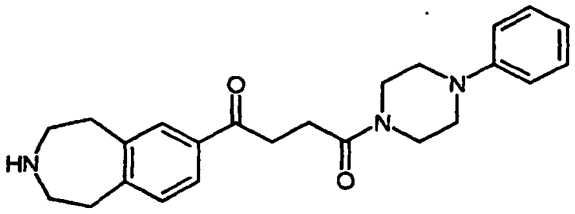


[0647] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 482

Example 114

4-Oxo-4-(4-phenylpiperazin-1-yl)-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0648]

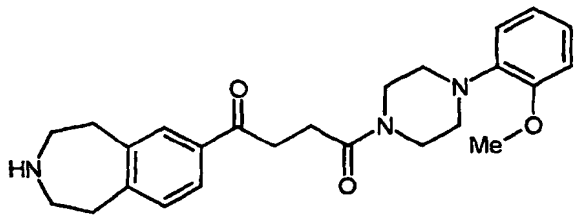


[0649] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1): 392

Example 115

4-[4-(2-Methoxyphenyl)piperazin-1-yl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0650]

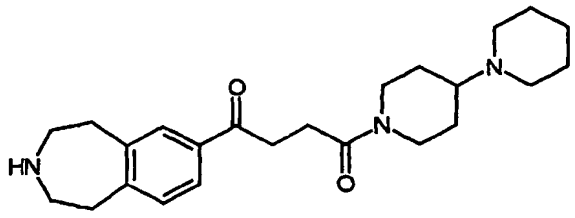


[0651] The title compound was obtained in the same manner as in Example 36.
MS (EST) (M+1) : 432

Example 116

4-(1,4'-Bipiperidin-1'-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0652]

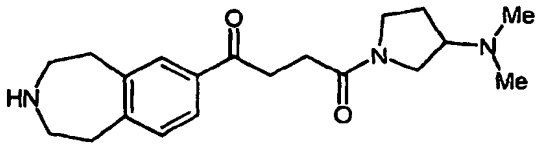


[0653] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 398

Example 117

4-[3-(Dimethylamino)pyrrolidin-1-yl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0654]

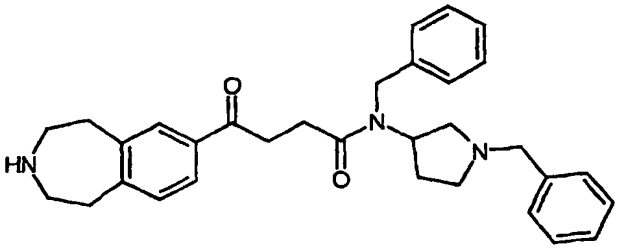


[0655] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 344

Example 118

N-Benzyl-N-(1-benzylpyrrolidin-3-yl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0656]

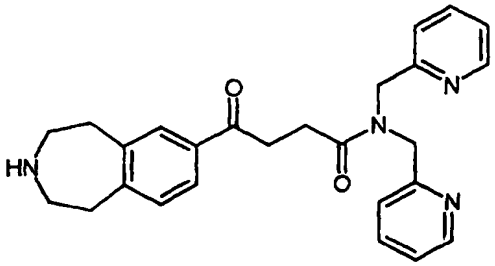


[0657] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 496

Example 119

4-Oxo-N,N-bis(pyridin-2-ylmethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0658]

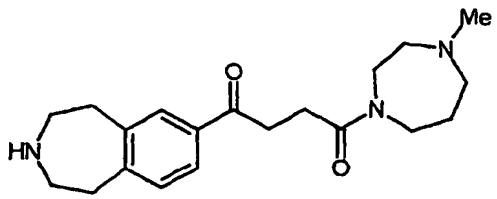


[0659] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 429

Example 120

4-(4-Methyl-1,4-diazepin-1-yl)-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0660]

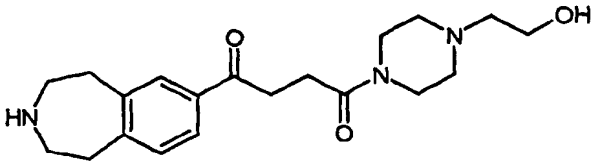


[0661] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1): 344

Example 121

4-[4-(2-Hydroxyethyl)pyrazin-1-yl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0662]

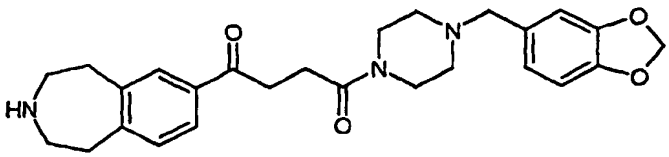


[0663] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 360

Example 122

4-[4-(1,3-Benzodioxol-5-ylmethyl)pyrazin-1-yl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0664]

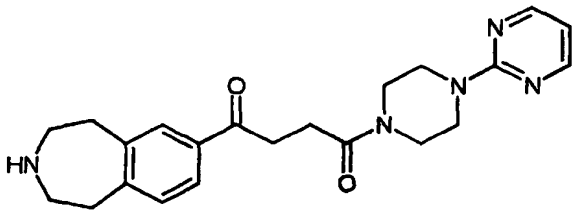


[0665] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 450

Example 123

4-Oxo-4-[4-(pyrimidin-2-yl)piperazin-1-yl]-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0666]

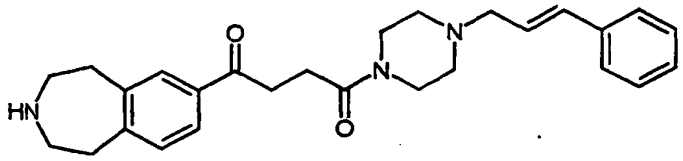


[0667] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 394

Example 124

4-Oxo-4-[4-[(2E)-3-phenyl-2-propenyl]piperazin-1-yl]-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0668]

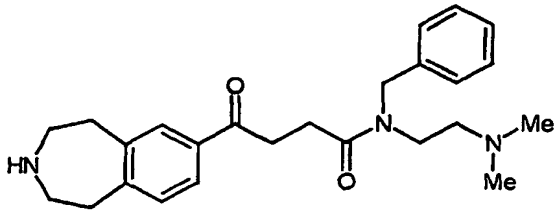


[0669] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 432

Example 125

N-Benzyl-N-[2-(dimethylamino)ethyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0670]

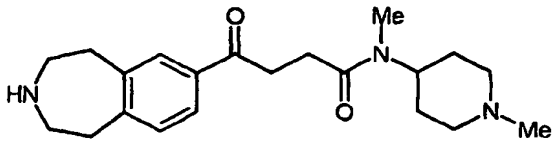


[0671] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1): 408

Example 126

N-Methyl-N-(1-methylpiperazin-4-yl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0672]

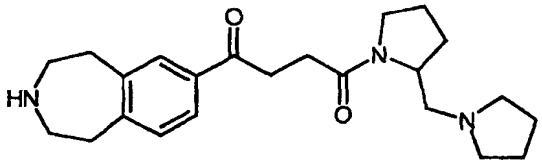


[0673] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 358

Example 127

4-Oxo-4-[2-(pyrrolidin-1-ylmethyl)pyrrolidin-1-yl]-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0674]

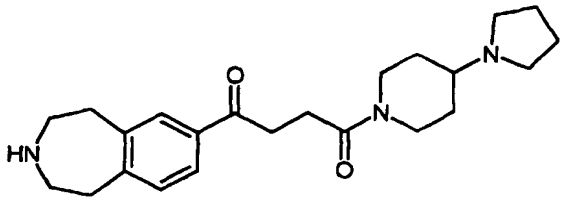


[0675] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 384

Example 128

4-Oxo-4-[4-(pyrrolidin-1-yl)piperidin-1-yl]-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butan-1-one trifluoroacetate

[0676]

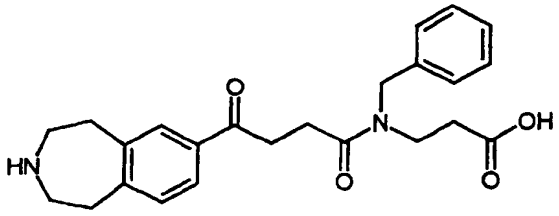


[0677] The title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 384

Example 129

N-Benzyl-N-(2-carboxyethyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide trifluoroacetate

[0678]

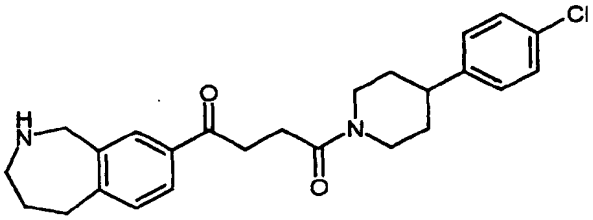


[0679] The title compound was obtained in the same manner as in Example 36.
MS (ESI) (M+1) : 409

Example 130

4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)-1-butanone

[0680]

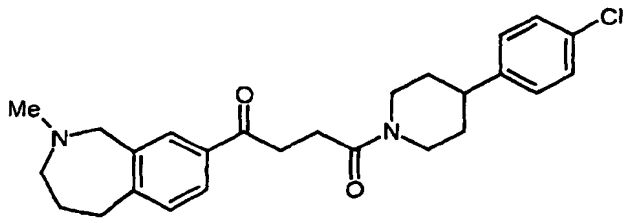


1) Using 2-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-2-benzazepine, 4-oxo-4-[2-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl]butanoic acid was obtained by the same procedure as in Reference Example 15.
^{1}H-NMR (DMSO-d_6) δ: 1.82 (2H, m) , 2.58 (2H, t, J = 6.2 Hz), 3.08 (2H, m), 3.23 (2H, t, J = 6.0 Hz), 3.89 (2H, m), 4.73 (2H, m), 7.37-7.41 (1H, m), 7.84-7.88 (2H, m), 12.16 (1H, s) .
2) Using 4-oxo-4-[2-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl]butanoic acid obtained in 1) above, the title compound was obtained as colorless powder by the same procedures as in Examples 12 and 13.
^{1}H-NMR ($CDCl_3$) δ: 1.57-1.90 (6H, m), 2.60-2.74 (3H, m), 2.82 (2H, t, J = 6.6 Hz), 2.99 (2H, m), 3.12-3.24 (3H, m), 3.34 (2H, t, J = 6.6 Hz), 4.01 (2H, s), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.12-7.30 (5H, m), 7.79 (2H, m).
Melting point: 122-124 °C (crystallizing solvent: ethanol-diisopropyl ether).

Example 131

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(2-methyl-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)-4-oxo-1-butanone

[0681]



[0682] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)-1-butanone obtained in Example 130, the title compound was obtained as colorless powder by the same procedure as in Example 16.

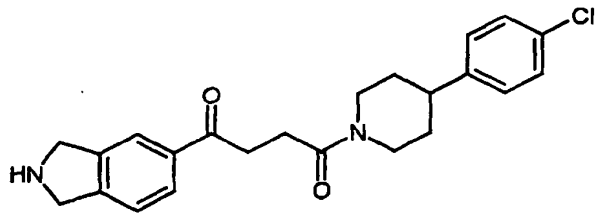
^{1}H-NMR ($CDCl_3$) δ: 1.57-1.94 (6H, m), 2.33 (3H, s), 2.61-2.70 (2H, m) , 2.84 (2H, t, J = 6.6 Hz), 3.00 (2H, m), 3.02 (2H, t, J = 5.1 Hz), 3.18 (1H, m), 3.36 (2H, t, J = 6.6 Hz), 3.85 (2H, s), 4.14 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.12-7.30 (5H, m), 7.83 (2H, m).

Melting point: 133-134 °C (crystallizing solvent: ethanol-diisopropyl ether).

Example 132

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(2,3-dihydro-1H-isoindol-5-yl)-4-oxo-1-butanone

[0683]



1) Using 2-(trifluoroacetyl) isoindole, 4-oxo-4-[2-(trifluoroacetyl)-2,3-dihydro-1H-isoindol-5-yl]butanoic acid was obtained by the same procedure as in Reference Example 15.

^{1}H-NMR (DMSO-d_6) δ: 2.59 (2H, t, J = 6.2 Hz), 3.25 (2H, t, J = 6.0 Hz), 4.90 (2H, m), 5.12 (2H, m), 7.55 (1H, m), 7.96-8.05 (2H, m), 12.16 (1H, s).

2) Using 4-oxo-4-[2-(trifluoroacetyl)-2,3-dihydro-1H-isoindol-5-yl]butanoic acid obtained in 1) above, the title compound was obtained as colorless powder by the same procedures as in Examples 12 and 13.

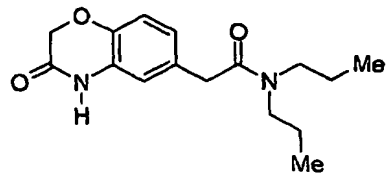
^{1}H-NMR ($CDCl_3$) δ: 1.56-1.68 (2H, m), 1.82-1.96 (2H, m), 2.58-2.74 (2H, s), 2.84 (2H, t, J = 6.6 Hz), 3.04 (1H, s), 3.17 (1H, m), 3.36 (2H, t, J = 6.6 Hz), 4.15 (1H, d, J = 15.6 Hz), 4.31 (4H, s), 4.76 (1H, d, J = 12 Hz), 7.11-7.36 (5H, m), 7.92 (2H, m).

Melting point: 133-134 °C (crystallizing solvent: ethanol-diisopropyl ether).

Example 133

N,N-Dipropyl-(3,4-dihydro-2H-1,4-benzoxazine-3-oxo-6-yl) acetamide

[0684]



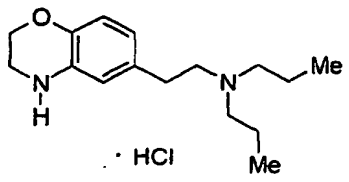
[0685] 10 % palladium-carbon (2.5 g) was added to a solution of N,N-dipropyl-(4-ethoxycarbonylmethoxy-3-nitrophenyl) acetamide (11 g, 30.0 mmol) obtained in Reference Example 17 in ethanol (500 ml) and then subjected to catalytic hydrogenation reaction at normal pressure at room temperature. After the reaction was finished, the catalyst was filtered off, and the resultant filtrate was concentrated. The residues were dissolved in toluene (500 ml) and heated overnight under reflux. The reaction solution was concentrated and then recrystallized from ethyl acetate-hexane, whereby the title compound (8.4 g) was obtained as crystals with a mp of 121 to 122 °C.
^{1}H-NMR ($CDCl_3$) δ: 0.8-1.0 (6H, m), 1.4-1.7 (4H, m), 3.15-3.4 (4H, m), 3.62 (2H, s), 4.53 (2H, s), 6.7-6.9 (3H, m), 9.1-9.4 (1H, br).

Elemental analysis for $C_{16}H_{22}N_2O_3$			
Calcd.	C, 66.18;	H, 7.64;	N, 9.65.
Found	C, 66.07;	H, 7.37;	N, 9.59.

Example 134

3,4-Dihydro-6-[2-(N,N-dipropylamino)ethyl]-2H-1,4-benzoxazine hydrochloride

[0686]

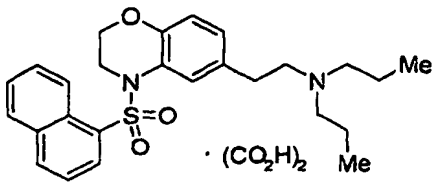


[0687] 1 N borane/THF solution (140 ml, 140 mmol) was added to a solution of N,N-dipropyl-(3,4-dihydro-2H-1,4-benzoxazine-3-oxo-6-yl)acetamide (10 g, 34.4 mmol) obtained in Example 133 in THF (200 ml), and the mixture was stirred at room temperature for 4 hours, and then 6 N hydrochloric acid (30 ml, 180 mmol) was added dropwise to the reaction solution under cooling with ice-bath. The reaction solution was neutralized with 6 N aqueous sodium hydroxide and extracted with ethyl acetate. The reaction solution was washed with water, dried over anhydrous magnesium sulfate and concentrated. The residues were purified by silica gel column chromatography (developing solvent; hexane : ethyl acetate = 4 : 1), then 4 N hydrochloric acid in ethyl acetate was added thereto, and the solution was concentrated, whereby the title compound (6.8 g) was obtained as amorphous powder.
^{1}H-NMR ($CDCl_3$, free base) δ: 0.91 (6H, t, J = 7.2 Hz), 1.6-1.8 (4H, m), 2.6-2.8 (4H, m), 2.84 (4H, brs), 3.41 (2H, t, J = 4.4 Hz), 3.6-4.0 (1H, br), 4.22 (2H, t, J = 4.4 Hz), 6.4-6.6 (2H, m), 6.65-6.75 (1H, m).

Example 135

3,4-Dihydro-6-[2-(N,N-dipropylamino)ethyl]-4-(1-naphthalenesulfonyl)-2H-1,4-benzoxazine succinate

[0688]

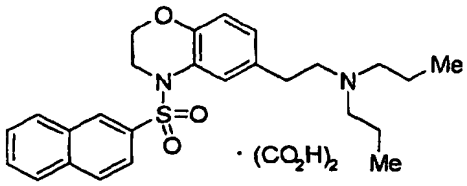


[0689] A solution of 1-naphthalenesulfonyl chloride (388 mg, 1.72 mmol) in acetonitrile (5 ml) was added to a solution of 3,4-dihydro-6-[2-(N,N-propylamino)ethyl]-2H-1,4-benzoxazine hydrochloride (300 mg, 1.14 mmol) obtained in Example 134, 4-dimethylaminopyridine (140 mg, 1.14 mmol) and triethylamine (0.48 ml, 3.43 mmol) in acetonitrile (15 ml) under cooling with ice-bath, and the mixture was stirred at room temperature for 4 hours. Water (50 ml) was added to the reaction solution which was then extracted with ethyl acetate. The extract was washed with 10 % aqueous potassium carbonate and a saturated saline solution, dried over anhydrous sodium sulfate and concentrated. The residues were purified by silica gel column chromatography (developing solvent; ethyl acetate), and succinic acid (1 equivalent) was added thereto, and the product was recrystallized from ethyl acetate-diisopropyl ether, whereby the title compound (220 mg) was obtained as crystals with a mp of 144 to 145 °C.
^{1}H-NMR ($CDCl_3$, free base) δ: 0.89 (6H, t, J = 7.2 Hz), 1.4-1.6 (4H, m), 2.4-2.6 (4H, m), 2.66 (4H, brs), 3.65 (2H, t, J = 4.6 Hz), 3.89 (2H, t, J = 4.6 Hz), 6.64 (1H, d, J = 8.4 Hz), 6.89 (1H, dd, J = 8.4, 1.8 Hz), 7.3-7.6 (4H, m), 7.90 (1H, d, J = 7.8 Hz), 8.08 (1H, d, J = 8.4 Hz), 8.2-8.4 (2H, m).

Example 136

3,4-Dihydro-6-[2-(N,N-dipropylamino)ethyl]-4-(2-naphthalenesulfonyl)-2H-1,4-benzoxazine succinate

[0690]

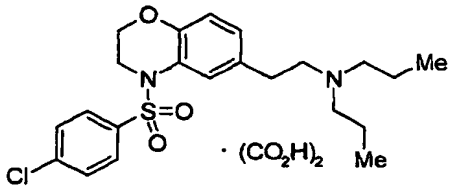


[0691] Using 3,4-dihydro-6-[2-(N,N-dipropylamino)ethyl]-2H-1,4-benzoxazine hydrochloride obtained in Example 134, the title compound was obtained as colorless amorphous powder by the same procedure as in Example 135.
^{1}H-NMR ($CDCl_3$, free base) δ: 0.90 (6H, t, J = 7.2 Hz), 1.4-1.6 (4H, m) , 2.4-2.6 (4H, m), 2.71 (4H, brs), 3.68 (2H, t, J = 4.6 Hz), 3.93 (2H, t, J = 4.6 Hz), 6.68 (1H, d, J = 8.4 Hz), 6.90 (1H, dd, J = 8.4, 1.8 Hz), 7.5-7.8 (4H, m), 7.8-8.0 (3H, m), 8.29 (1H, brs).

Example 137

4-(4-Chlorobenzenesulfonyl)-3,4-dihydro-6-[2-(N,N-dipropylamino)ethyl]-2H-1,4-benzoxazine succinate

[0692]



[0693] Using 3,4-dihydro-6-[2-(N,N-dipropylamino)ethyl]-2H-1,4-benzoxazine hydrochloride obtained in Example 134, the title compound was obtained as powder by the same procedure as in Example 135.
^{1}H-NMR ($CDCl_3$, free base) δ: 0.89 (6H, t, J = 7.2 Hz), 1.4-1.6 (4H, m), 2.4-2.6 (4H, m), 2.69 (4H, brs), 3.72 (2H, t, J = 4.6 Hz), 3.88 (2H, t, J = 4.6 Hz), 6.72 (1H, d, J = 8.4 Hz), 6.92 (1H, dd, J = 8.6, 2.0 Hz), 7.41 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.8 Hz), 7.64 (1H, d, J = 2.0 Hz).

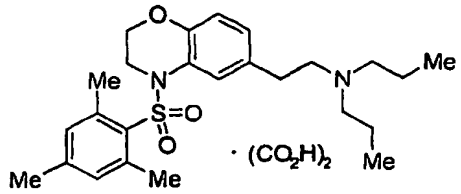
Elemental analysis for $C_{24}H_{31}ClN_2O_7S$			
Calcd.	C, 54.70;	H, 5.93;	N, 5.32.
Found	C, 54.46;	H, 5.88;	N, 5.29.

Melting point: 130-133 °C (crystallizing solvent: acetone)

Example 138

3,4-Dihydro-6-[2-(N,N-dipropylamino)ethyl]-4-(2,4,6-trimethylbenzenesulfonyl)-2H-1,4-benzoxazine succinate

[0694]

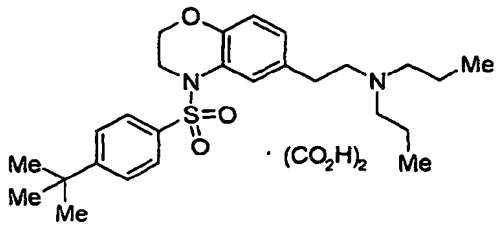


[0695] Using 3,4-dihydro-6-[2-(N,N-dipropylamino)ethyl]-2H-1,4-benzoxazine hydrochloride obtained in Example 134, the title compound was obtained as powder by the same procedure as in Example 135.
^{1}H-NMR ($CDCl_3$, free base) δ: 0.88 (6H, t, J = 7.4 Hz), 1.3-1.6 (4H, m), 2.3-2.6 (4H, m), 2.33 (3H, s), 2.48 (4H, brs), 2.57 (6H, s), 3.83 (2H, t, J = 4.6 Hz), 4.23 (2H, t, J = 4.6 Hz), 6.61 (1H, brs), 6.8-6.85 (2H, m), 7.00 (2H, s).
Melting point: 157-158 °C (crystallizing solvent: ethyl acetate-diisopropyl ether)

Example 139

4-(4-t-Butylbenzenesulfonyl)-3,4-dihydro-6-[2-(N,N-dipropylamino)ethyl]-2H-1, 4-benzoxazine succinate

[0696]



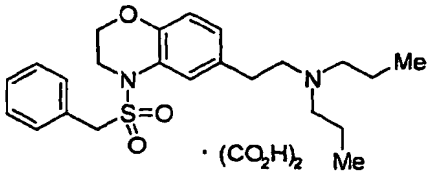
[0697] Using 3,4-dihydro-6-[2-(N,N-dipropylamino)ethyl]-2H-1,4-benzoxazine hydrochloride obtained in Example 134, the title compound was obtained as amorphous powder by the same procedure as in Example 135.
^{1}H-NMR ($CDCl_3$, free base) δ: 0.90 (6H, t, J = 7.2 Hz), 1.30 (9H, s), 1.3-1.6 (4H, m), 2.4-2.55 (4H, m), 2.69 (4H, s), 3.71 (2H, t, J = 4.0 Hz), 3.85 (2H, t, J = 4.0 Hz), 6.72 (1H, d, J = 8.2 Hz), 6.90 (1H, dd, J = 8.2, 2.0 Hz), 7.44 (2H, d, J = 8.8 Hz), 7.57 (2H, d, J = 8.8 Hz), 7.68 (1H, d, J = 2.0 Hz).

Elemental analysis for $C_{28}H_{40}N_2O_7S$			
Calcd.	C, 61.29;	H, 7.35;	N, 5.11.
Found	C, 61.02;	H, 7.57;	N, 5.00.

Example 140

4-Benzylsulfonyl-3,4-dihydro-6-[2-(N,N-dipropylamino)ethyl]-2H-1,4-benzoxazine succinate

[0698]

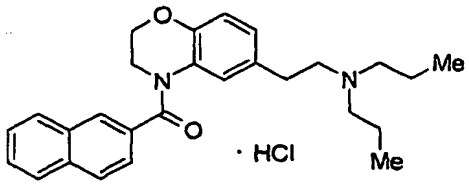


[0699] Using 3,4-dihydro-6-[2-(N,N-dipropylamino)ethyl]-2H-1,4-benzoxazine hydrochloride obtained in Example 134, the title compound was obtained as powder by the same procedure as in Example 135.
^{1}H-NMR ($CDCl_3$, free base) δ: 0.89 (6H, t, J = 7.2 Hz), 1.4-1.6 (4H, m), 2.4-2.55 (4H, m), 2.66 (4H, brs), 3.53 (2H, t, J = 4.2 Hz), 3.73 (2H, t, J = 4.2 Hz), 4.44 (2H, s), 6.7-7.0 (2H, m), 7.1-7.4 (6H, m).
Melting point: 150-151 °C (crystallizing solvent: ethyl acetate-diisopropyl ether)

Example 141

3,4-Dihydro-6-[2-(N,N-dipropylamino)ethyl]-4-(2-naphthoyl)-2H-1,4-benzoxazine hydrochloride

[0700]

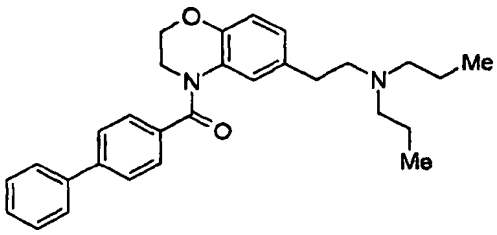


[0701] Using 3,4-dihydro-6-[2-(N,N-dipropylamino)ethyl]-2H-1,4-benzoxazine hydrochloride obtained in Example 134, the title compound was obtained as powder by the same procedure as in Example 135.
^{1}H-NMR ($CDCl_3$, free base) δ: 0.75 (6H, t, J = 7.2 Hz), 1.0-1.4 (4H, m), 1.9-2.2 (6H, m), 2.2-2.4 (2H, m), 4.06 (2H, t, J = 4.2 Hz), 4.39 (2H, t, J = 4.2 Hz), 6.5-6.9 (3H, m), 7.4-7.6 (3H, m), 7.7-7.9 (3H, m), 8.04 (1H, s).
Melting point: 165-166 °C (crystallizing solvent: methanol-diethyl ether)

Example 142

4-(4-Biphenyl-1-carbonyl)-3,4-dihydro-6-[2-(N,N-dipropylamino)ethyl]-2H-1,4-benzoxazine

[0702]

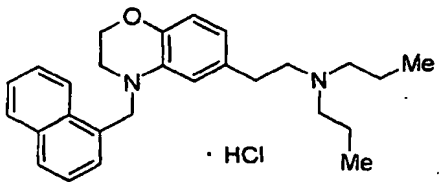


[0703] Using 3,4-dihydro-6-[2-(N,N-dipropylamino)ethyl]-2H-1,4-benzoxazine hydrochloride obtained in Example 134, the title compound was obtained as powder by the same procedure as in Example 135.
^{1}H-NMR ($CDCl_3$) δ: 0.75 (6H, t, J = 7.2 Hz), 1.1-1.4 (4H, m), 2.1-2.6 (8H, m), 4.04 (2H, t, J = 4.6 Hz), 4.38 (2H, t, J = 4.6 Hz), 6.6-6.9 (3H, m), 7.3-7.5 (3H, m), 7.5-7.7 (6H, m).
Melting point: 95-96 °C (crystallizing solvent: ethyl acetate-diisopropyl ether)

Example 143

3,4-Dihydro-6-[2-(N,N-dipropylamino)ethyl]-4-(1-naphthylmethyl)-2H-1,4-benzoxazine hydrochloride

[0704]



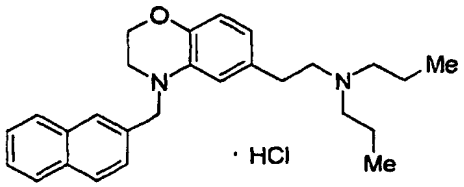
[0705] Potassium carbonate (316 mg, 2.29 mmol) was added to a solution of 3,4-dihydro-6-[2-(N,N-dipropylamino) ethyl]-2H-1,4-benzoxazine hydrochloride (200 mg, 0.76 mmol) obtained in Example 134 and 1-chloromethyl naphthalene (400 mg, 2.29 mmol) in DMF (15 ml). After the reaction solution was stirred at room temperature for 2 hours, water was added to the reaction solution which was then extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated. The residues were purified by silica gel column chromatography (developing solvent; hexane : ethyl acetate = 3 : 1), treated with 4 N hydrochloric acid in ethyl acetate and crystallized from acetone-pentane, whereby the title compound (80 mg) was obtained as crystals with a mp of 177 to 178 °C.
^{1}H-NMR ($CDCl_3$, free base) δ: 0.82 (6H, t, J = 7.4 Hz), 1.4-1.7 (4H, m), 2.3-2.5 (4H, m), 2.59 (4H, brs), 3.28 (2H, t, J = 4.4 Hz), 4.21 (2H, t, J = 4.4 Hz), 4.84 (2H, s), 6.4-6.6 (2H, m), 6.7-6.8 (1H, m), 7.3-7.6 (4H, m), 7.7-8.0 (2H, m), 8.0-8.1 (1H, m).

Elemental analysis for $C_{27}H_{35}ClN_2O \cdot 0.5H_2O$			
Calcd.	C, 72.38;	H, 8.10;	N, 6.25.
Found	C, 72.24;	H, 7.91;	N, 6.12.

Example 144

3,4-Dihydro-6-[2-(N,N-dipropylamino)ethyl]-4-(2-naphthylmethyl)-2H-1,4-benzoxazine hydrochloride

[0706]

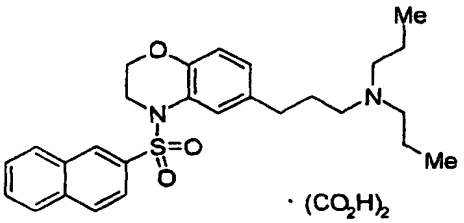


[0707] Using 3,4-dihydro-6-[2-(N,N-dipropylamino) ethyl]-2H-1,4-benzoxazine hydrochloride obtained in Example 134, the title compound was obtained as powder by the same procedure as in Example 143.
^{1}H-NMR ($CDCl_3$, free base) δ: 0.82 (6H, t, J = 7.4 Hz), 1.4-1.7 (4H, m), 2.4-2.9 (8H, m), 3.3-3.5 (2H, m), 4.2-4.4 (2H, m) , 4.59 (2H, brs), 6.4-6.6 (2H, m) , 6.7-6.8 (1H, m) , 7.3-7.5 (3H, m), 7.7-7.9 (4H, m).
Melting point: 169-170 °C (crystallizing solvent: diethyl ether-hexane)

Example 145

3,4-Dihydro-6-[3-(N,N-dipropylamino)propyl]-4-(2-naphthalenesulfonyl)-2H-1,4-benzoxazine succinate

[0708]



[0709] Potassium carbonate (0.9 g, 6.48 mmol) was added to a solution of 3,4-dihydro-6-(3-iodopropyl)-4-(2-naphthalenesulfonyl)-2H-1,4-benzoxazine (1.0 g, 2.16 mmol) obtained in Reference Example 19 and dipropylamine (263 mg, 2.60 mmol) in DMF (20 ml), and the mixture was stirred overnight at room temperature. Water was added to the reaction solution which was then extracted with ethyl acetate. The extract was washed with water and aqueous satu-

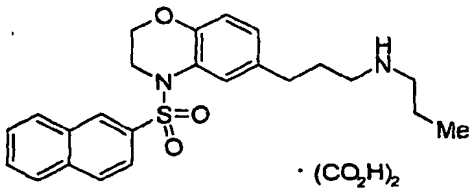
rated sodium bicarbonate, dried over anhydrous sodium sulfate and concentrated. The residues were purified by alumina column chromatography (developing solvent; hexane : ethyl acetate = 4 : 1) and then dissolved in ethyl acetate. 1 equivalent of succinic acid was added to the resultant solution, and then the solvent was distilled away, whereby the title compound (1.17 g) was obtained as amorphous powder.

^{1}H-NMR ($CDCl_3$, free base) δ: 0.8-1.0 (6H, m), 1.3-1.6 (4H, m) , 1.6-1.9 (2H, m), 2.3-2.6 (8H, m), 3.67 (2H, t, J = 4.6 Hz), 3.92 (2H, t, J = 4.6 Hz), 6.68 (1H, d, J = 8.4 Hz), 6.91 (1H, dd, J = 8.4, 2.0 Hz), 7.52 (1H, dd, J = 8.4, 2.0 Hz), 7.5-7.5 (2H, m), 7.76 (1H, d, J = 2.0 Hz), 7.8-8.0 (3H, m) , 8.28 (1H, d, J = 1.8 Hz).

Example 146

3,4-Dihydro-4-(2-naphthalenesulfonyl)-6-[3-(N-propylamino)propyl]-2H-1,4-benzoxazine succinate

[0710]



[0711] Using 3,4-dihydro-6-(3-iodopropyl)-4-(2-naphthalene sulfonyl)-2H-1,4-benzoxazine obtained in Reference Example 19, the title compound was obtained as powder by the same procedure as in Example 145.

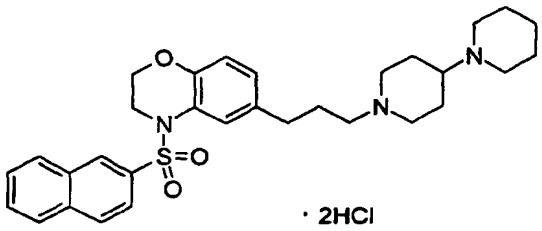
^{1}H-NMR ($CDCl_3$, free base) δ: 0.92 (3H, t, J = 7.4 Hz), 1.4-1.7 (2H, m) , 1.7-2.0 (4H, m) , 2.5-2.8 (4H, m) , 3.68 (2H, t, J = 4.6 Hz), 3.92 (2H, t, J = 4.6 Hz), 6.68 (1H, d, J = 8.4 Hz), 6.89 (1H, dd, J = 8.4, 2.2 Hz), 7.4-7.7 (3H, m) , 7.74 (1H, d, J = 1.8 Hz), 7.8-8.0 (3H, m) , 8.28 (1H, d, J = 1.6 Hz).

Melting point: 155-156 °C (crystallizing solvent: methanol-diethyl ether)

Example 147

3,4-Dihydro-4-(2-naphthalenesulfonyl)-6-[3-(4-piperidinopiperidino)propyl]-2H-1,4-benzoxazine dihydrochloride

[0712]



[0713] Using 3,4-dihydro-6-(3-iodopropyl)-4-(2-naphthalene sulfonyl)-2H-1,4-benzoxazine obtained in Reference Example 19, the title compound was obtained as powder by the same procedure as in Example 145.

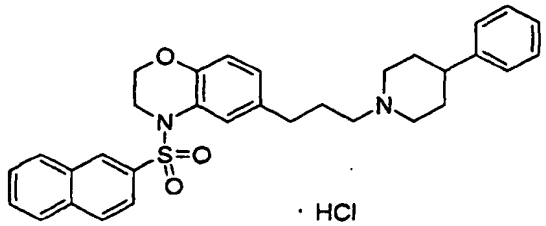
^{1}H-NMR ($CDCl_3$, free base) δ: 1.3-2.0 (13H, m), 2.1-2.4 (4H, m), 2.4-2.7 (6H, m) , 2.9-3.1 (2H, m) , 3.68 (2H, d, J = 4.6 Hz), 3.91 (2H, d, J = 4.6 Hz), 6.68 (1H, d, J = 8.2 Hz), 6.89 (1H, dd, J = 8.2, 2.0 Hz), 7.4-7.7 (3H, m), 7.74 (1H, d, J = 2.0 Hz), 7.8-8.0 (3H, m), 8.28 (1H, d, J = 1.6 Hz).

Melting point: 240-241 °C (crystallizing solvent: methanol-diethyl ether)

Example 148

3,4-Dihydro-4-(2-naphthalenesulfonyl)-6-[3-(4-phenylpiperidino)propyl]-2H-1,4-benzoxazine hydrochloride

[0714]

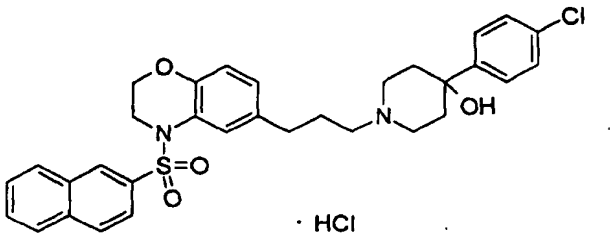


[0715] Using 3,4-dihydro-6-(3-iodopropyl)-4-(2-naphthalene sulfonyl)-2H-1,4-benzoxazine obtained in Reference Example 19, the title compound was obtained as powder by the same procedure as in Example 145.
^{1}H-NMR ($CDCl_3$, free base) δ: 1.6-2.2 (8H, m), 2.3-2.6 (3H, m), 2.64 (2H, t, J = 7.6 Hz), 3.0-3.2 (2H, m), 3.68 (2H, t, J = 4.6 Hz), 3.93 (2H, t, J = 4.6 Hz), 6.69 (1H, d, J = 8.4 Hz), 6.91 (1H, dd, J = 8.4, 2.0 Hz), 7.1-7.4 (5H, m) , 7.4-7.7 (3H, m), 7.76 (1H, d, J = 2.0 Hz), 7.8-8.0 (3H, m), 8.30 (1H, brs).
Melting point: 182-183 °C (crystallizing solvent: methanol-diethyl ether)

Example 149

6-[3-[4-(4-Chlorophenyl)-4-hydroxypiperidino]propyl]-3,4-dihydro-4-(2-naphthalenesulfonyl)-2H-1,4-benzoxazine hydrochloride

[0716]

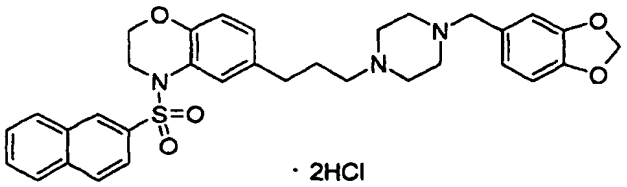


[0717] Using 3,4-dihydro-6-(3-iodopropyl)-4-(2-naphthalene sulfonyl)-2H-1,4-benzoxazine obtained in Reference Example 19, the title compound was obtained as powder by the same procedure as in Example 145.
^{1}H-NMR ($CDCl_3$) δ: 1.7-2.0 (4H, m) , 2.15 (2H, td, J = 13.2, 4.4 Hz), 2.3-2.6 (4H, m), 2.65 (2H, t, J = 7.6 Hz), 2.7-2.9 (2H, m), 3.67 (2H, t, J = 4.6 Hz), 3.92 (2H, t, J = 4.6 Hz), 6.70 (1H, d, J = 8.4 Hz), 6.91 (1H, dd, J = 8.4, 1.8 Hz), 7.2-7.4 (2H, m), 7.4-7.7 (7H, m), 7.77 (1H, d, J = 2.0 Hz), 7.8-8.0 (3H, m), 8.29 (1H, brs).
Melting point: 125-126 °C (crystallizing solvent: methanol-diethyl ether)

Example 150

3,4-Dihydro-6-[3-[4-(3,4-methylenedioxybenzyl)piperazino]propyl]-4- (2-naphthalenesulfonyl)-2H-1,4-benzoxazine dihydrochloride

[0718]

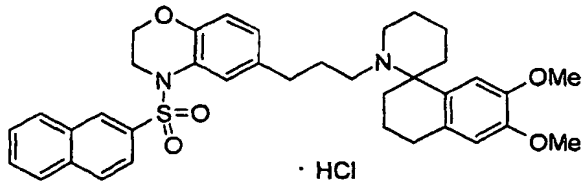


[0719] Using 3,4-dihydro-6-(3-iodopropyl)-4-(2-naphthalene sulfonyl)-2H-1,4-benzoxazine obtained in Reference Example 19, the title compound was obtained as powder by the same procedure as in Example 145.
^{1}H-NMR ($CDCl_3$, free base) δ: 1.7-1.9 (2H, m) , 2.3-2.7 (12H, m) , 3.42 (2H, s), 3.68 (2H, t, J = 4.6 Hz), 3.92 (2H, t, J = 4.6 Hz), 5.94 (2H, s), 6.68 (1H, d, J = 8.4 Hz), 6.75 (2H, brs), 6.8-7.0 (2H, m), 7.4-7.7 (3H, m), 7.74 (1H, d, J = 2.0 Hz), 7.8-8.0 (3H, m), 8.28 (1H, d, J = 1.6 Hz).
Melting point: 212-213 °C (crystallizing solvent: methanol-diethyl ether)

Example 151

3,4-Dihydro-4-[3,4-dihydro-6,7-dimethoxyspiro[naphthalene-2(1H),2'-piperidine]-2'-yl]-4-(2-naphthalenesulfonyl)-2H-1,4-benzoxazine hydrochloride

[0720]

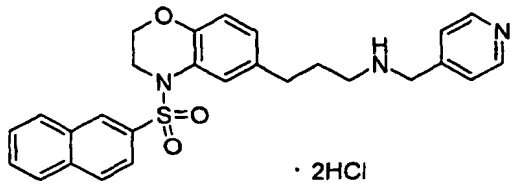


[0721] Using 3,4-dihydro-6-(3-iodopropyl)-4-(2-naphthalene sulfonyl)-2H-1,4-benzoxazine obtained in Reference Example 19, the title compound was obtained as amorphous powder by the same procedure as in Example 145.
^{1}H-NMR ($CDCl_3$, free base) δ: 1.3-2.0 (10H, m), 2.3-2.9 (10H, m), 3.66 (2H, t, J = 4.4 Hz), 3.82 (6H, s), 3.90 (2H, t, J = 4.4 Hz), 6.56 (2H, brs), 6.68 (1H, d, J = 8.4 Hz), 6.90 (1H, dd, J = 8.4, 2.0 Hz), 7.47 (1H, dd, J = 8.6, 2.0 Hz), 7.5-7.7 (2H, m), 7.7-8.0 (4H, m), 8.27 (1H, brs).

Example 152

3,4-Dihydro-4-(2-naphthalenesulfonyl)-6-[3-(4-pyridylmethylamino)propyl]-2H-1,4-benzoxazine dihydrochloride

[0722]

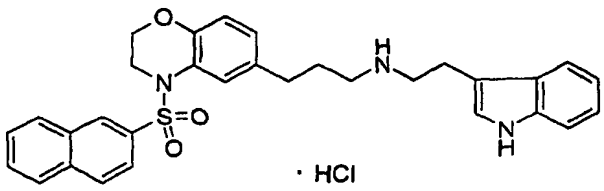


[0723] Using 3,4-dihydro-6-(3-iodopropyl)-4-(2-naphthalene sulfonyl)-2H-1,4-benzoxazine obtained in Reference Example 19, the title compound was obtained as amorphous powder by the same procedure as in Example 145. ^{1}H-NMR ($CDCl_3$, free base) δ: 1.7-2.0 (2H, m) , 2.67 (4H, t, J = 7.0 Hz), 3.68 (2H, t, J = 4.4 Hz), 3.81 (2H, s), 3.91 (2H, t, J = 4.4 Hz), 6.68 (1H, d, J = 8.4 Hz), 6.88 (1H, dd, J = 8.4, 2.2 Hz), 7.1-7.3 (2H, m), 7.4-7.7 (3H, m), 7.7-8.0 (4H, m), 8.28 (1H, brs), 8.53 (2H, d, J = 6.2 Hz).

Example 153

6-{3-[2-(3-Indolylethyl)amino]propyl}-3,4-dihydro-4-(2-naphthalenesulfonyl)-2H-1,4-benzoxazine hydrochloride

[0724]

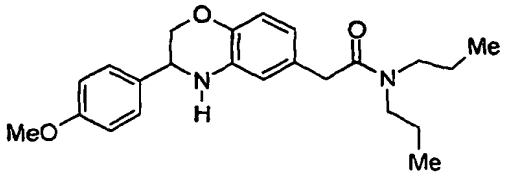


[0725] Using 3,4-dihydro-6-(3-iodopropyl)-4-(2-naphthalene sulfonyl)-2H-1,4-benzoxazine obtained in Reference Example 19, the title compound was obtained as amorphous powder by the same procedure as in Example 145. ^{1}H-NMR ($CDCl_3$, free base) δ: 1.7-2.0 (2H, m) , 2.58 (2H, t, J = 8.0 Hz), 2.69 (2H, t, J = 8.0 Hz), 2.8-3.1 (4H, m), 3.67 (2H, t, J = 4.4 Hz), 3.90 (2H, t, J = 4.4 Hz), 6.64 (1H, d, J = 8.4 Hz), 6.82 (1H, dd, J = 8.2, 2.0 Hz), 7.0-7.3 (3H, m), 7.3-7.4 (1H, m), 7.4-7.8 (5H, m), 7.8-8.0 (3H, m), 8.18 (1H, brs), 8.27 (1H, brs).

Example 154

N,N-Dipropyl-[3,4-dihydro-3-(4-methoxyphenyl)-2H-1,4-benzoxazin-6-yl]acetamide

[0726]



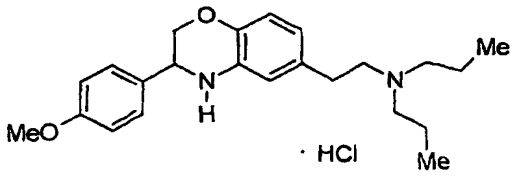
[0727] Using N,N-dipropyl-[4-(4-methoxybenzene) carbonylmethoxy-3-nitrophenyl]acetamide obtained in Reference Example 20, the title compound was obtained as oily matter by the same procedure as in Example 133.
^{1}H-NMR ($CDCl_3$) δ: 0.8-1.0 (6H, m), 1.4-1.7 (4H, m) , 3.1-3.4 (4H, m), 3.56 (2H, s), 3.82 (3H, s), 3.8-4.0 (2H, m), 4.22 (1H, d, J = 10.6 Hz), 4.44 (1H, dd, J = 8.8, 3.0 Hz), 6.52 (1H, dd, J = 8.2, 2.2 Hz), 6.60 (1H, d, J = 2.2 Hz), 6.74 (1H, d, J = 8.2 Hz), 6.91 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.8 Hz).

Elemental analysis for $C_{23}H_{30}N_2O_3$			
Calcd.	C, 72.22;	H, 7.91;	N, 7.32.
Found	C, 71.91;	H, 8.10;	N, 7.35.

Example 155

3,4-Dihydro-6-[2-(N,N-dipropylamino)ethyl]-3-(4-methoxyphenyl)-2H-1,4-benzoxazine hydrochloride

[0728]

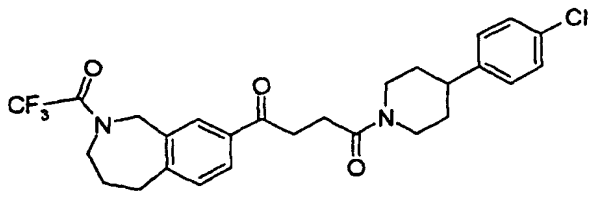


[0729] Using N,N-dipropyl-[3,4-dihydro-3-(4-methoxyphenyl)-2H-1,4-benzoxazin-6-yl]acetamide obtained in Example 154, the title compound in the form of a free base was obtained as powder with a mp of 85 to 90 °C by the same procedure as in Example 133. 4 N hydrochloric acid in ethyl acetate was added to the resultant powder which was then concentrated, whereby the title compound was obtained as amorphous powder. ^{1}H-NMR ($CDCl_3$, free base) δ: 0.91 (6H, t, J = 7.4 Hz), 1.5-1.8 (4H, m), 1.6-1.8 (4H, m), 2.87 (4H, s), 3.82 (3H, s), 3.8-4.0 (2H, m), 4.23 (1H, dd, J = 10.6, 3.0 Hz), 4.43 (1H, dd, J = 8.8, 3.0 Hz), 6.4-6.6 (2H, m), 6.77 (1H, d, J = 8.8 Hz), 6.91 (2H, d, J = 8.8 Hz), 7.30 (2H, d, J = 8.8 Hz).

Example 156

4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-[2-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-2-benzoxazin-8-yl]-1-butanone

[0730]

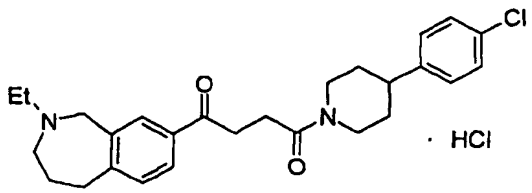


[0731] Using 4-oxo-4-[2-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl]butanoic acid obtained in 1) in Example 130, the title compound was obtained as powder by the same procedure as in Example 12.
^{1}H-NMR ($CDCl_3$) δ: 1.57-1.93 (6H, m), 2.61-2.81 (4H, m), 3.06 (2H, m), 3.22 (1H, m), 3.33 (2H, m), 3.94 (2H, m), 4.13 (1H, m), 4.68-4.79 (3H, m), 7.13 (2H, m), 7.29 (3H, m), 7.88 (1H, m), 8.03 (1H, m).
Melting point: 153-155 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 157

4-[4-(4-Chlorophenyl)piperidin-1-yl] -1-(2-ethyl-2,3,4,5-tetrahydro-1H-2-benzoxazin-8-yl)-4-oxobutan-1-one hydrochloride

[0732]



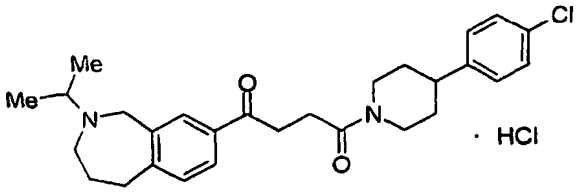
[0733] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)-1-butanone obtained in Example 130, the title compound was obtained as amorphous powder by the same procedure as in Example 17.

^{1}H-NMR (DMSO-d_6) δ: 1.27 (3H, t, J = 7.4 Hz), 1.42 (1H, m) , 1.63 (1H, m), 1.73-1.96 (4H, m), 2.51-2.89 (5H, m), 3.07 (4H, m), 3.22 (2H, m), 3.49 (2H, m), 4.10 (1H, m), 4.45-4.67 (3H, m), 7.27-7.46 (5H, m), 7.85 (2H, m), 10.47 (1H, m) .

Example 158

4-[4-(4-Chlorophenyl)piperidin-1-yl]-1-(2-isopropyl-2,3,4,5-tetrahydro-1H-2-benzoxazin-8-yl)-4-oxobutan-1-one hydrochloride

[0734]



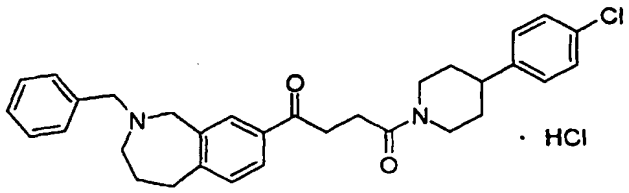
[0735] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl]-1-butanone obtained in Example 130, the title compound was obtained as amorphous powder by the same procedure as in Example 17.

^{1}H-NMR (DMSO-d_6) δ: 1.31-1.44 (6H, m), 1.55 (1H, m), 1.81-1.92 (3H, m), 2.07 (1H, m), 2.61 (1H, m), 2.74 (4H, m), 3.04 (1H, m), 3.24-3.30 (4H, m), 3.57 (3H, m), 4.08 (1H, m), 4.47-4.63 (3H, m), 7.24-7.46 (5H, m), 7.96 (2H, m), 9.89 (1H, m).

Example 159

1-(2-Benzyl-2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)-4-[4-(4-chlorophenyl)piperidin-1-yl]-4-oxobutan-1-one hydrochloride

[0736]



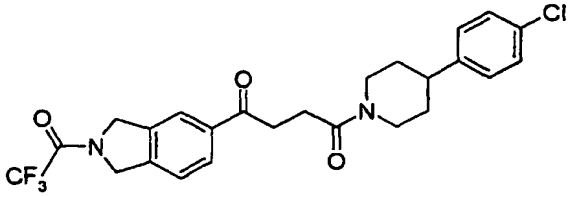
[0737] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-2-benzazepin-8-yl)-1-butanone obtained in Example 130, the title compound was obtained as amorphous powder by the same procedure as in Example 17.

^{1}H-NMR (DMSO-d_6) δ: 1.37 (1H, m), 1.58 (1H, m), 1.74-1.85 (3H, m), 2.07 (1H, m), 2.65-2.89 (5H, m), 3.07-3.21 (6H, m), 4.08 (2H, m), 4.40-4.50 (3H, m), 4.73 (1H, m), 7.28-7.61 (10H, m), 7.96 (2H, m), 10.84 (1H, m).

Example 160

4-[4-(4-Chlorophenyl)piperidin-1-yl]-4-oxo-1-[2-(trifluoroacetyl)-2,3-dihydro-1H-isoindol-5-yl]butan-1-one

[0738]



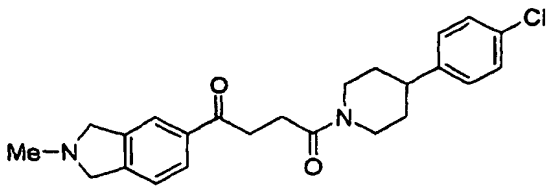
[0739] Using 4-oxo-4-[2-(trifluoroacetyl)-2,3-dihydro-1H-isoindol-5-yl]butanoic acid obtained in 1) in Example 132, the title compound was obtained as powder by the same procedure as in Example 12.

^{1}H-NMR ($CDCl_3$) δ: 1.58-1.67 (2H, m), 1.84-1.96 (2H, m), 2.62-2.75 (2H, m), 2.86 (2H, t, J = 6.6 Hz), 3.19 (1H, t, J = 11.7 Hz), 3.33 (2H, t, J = 6.6 Hz), 4.12 (1H, m), 4.75 (1H, m), 4.97 (2H, s), 5.09 (2H, m), 7.13-7.46 (5H, m), 7.96-8.04 (2H, m).

Example 161

4-[4-(4-Chlorophenyl)piperidin-1-yl]-1-(2-methyl-2,3-dihydro-1H-isoindol-5-yl)-4-oxobutan-1-one

[0740]

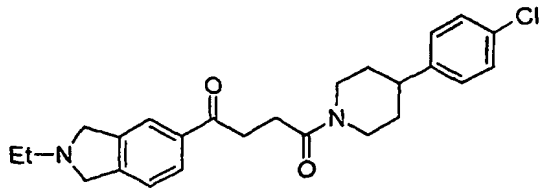


[0741] Using 4-[4-(4-chlorophenyl)piperidin-1-yl]-1-(2,3-dihydro-1H-isoindol-5-yl)-4-oxobutan-1-one obtained in Example 132, the title compound was obtained as powder by the same procedure as in Example 16.
^{1}H-NMR ($CDCl_3$) b: 1.56-1.68 (2H, m), 1.82-1.96 (2H, m), 2.63 (3H, s), 2.74 (2H, m), 2.84 (2H, t, J = 6.6 Hz), 3.17 (1H, m), 3.36 (2H, t, J = 6.6 Hz), 4.15 (1H, d, J = 15.6 Hz), 4.31 (4H, s), 4.76 (1H, d, J = 12 Hz), 7.11-7.36 (5H, m), 7.92 (2H, m).

Example 162

4-[4-(4-Chlorophenyl)piperidin-1-yl]-1-(2-ethyl-2,3-dihydro-1H-isoindol-5-yl)-4-oxobutan-1-one

[0742]

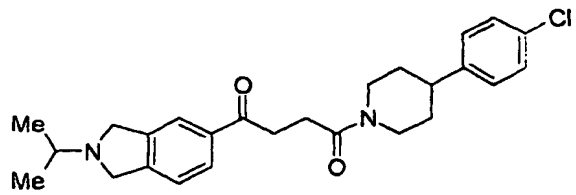


[0743] Using 4-[4-(4-chlorophenyl)piperidin-1-yl]-1-(2,3-dihydro-1H-isoindol-5-yl)-4-oxobutan-1-one obtained in Example 132, the title compound was obtained as powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J = 7.2 Hz), 1.26-1.62 (2H, m), 1.83-1.94 (2H, m), 2.61-2.80 (6H, m), 3.17 (1H, m), 3.36 (2H, t, J = 6.6 Hz), 3.96 (4H, s), 4.15 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.11-7.36 (5H, m), 7.88 (2H, m).

Example 163

4-[4-(4-Chlorophenyl)piperidin-1-yl]-1-(2-isopropyl-2,3-dihydro-1H-isoindol-5-yl)-4-oxobutan-1-one

[0744]



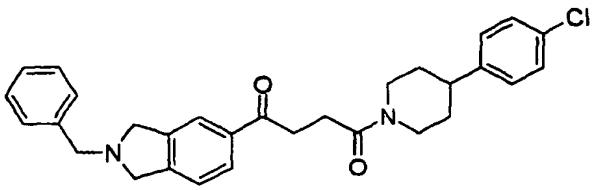
[0745] Using 4-[4-(4-chlorophenyl)piperidin-1-yl]-1-(2,3-dihydro-1H-isoindol-5-yl)-4-oxobutan-1-one obtained in Example 132, the title compound was obtained as powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 1.21 (6H, d, J = 5.4 Hz), 1.62-1.80 (2H, m), 1.83-1.94 (2H, m), 2.61-2.82 (5H, m), 3.17 (1H, m),

3.36 (2H, t, J = 6.6 Hz), 4.00 (4H, s), 4.15 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.11-7.36 (5H, m), 7.88 (2H, m).

Example 164

1-(2-Benzyl-2,3-dihydro-1H-isoindol-5-yl)-4-[4-(4-chlorophenyl)piperidin-1-yl]-4-oxobutan-1-one

[0746]

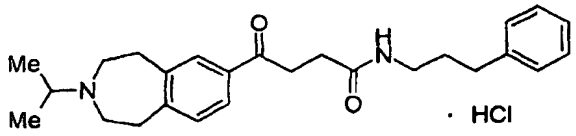


[0747] Using 4-[4-(4-chlorophenyl)-1-piperidin-1-yl]-1-(2,3-dihydro-1H-isoindol-5-yl)-4-oxobutan-1-one obtained in Example 132, the title compound was obtained as powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 1.62-1.80 (2H, m), 1.83-1.94 (2H, m), 2.59-2.82 (4H, m), 3.17 (1H, m) , 3.36 (2H, t, J = 6.6 Hz), 3.93 (2H, s), 3.97 (4H, s), 4.15 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.18, (2H, m), 7.29-7.42(8H, m), 7.88 (2H, m).

Example 165

4-(3-Isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-N-(3-phenylpropyl)butanamide hydrochloride

[0748]

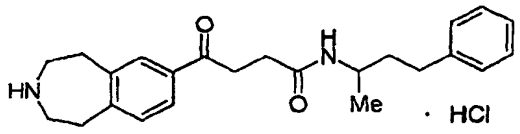


[0749] Using 4-oxo-N-(3-phenylpropyl)-4-(2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl)butanamide trifluoroacetate obtained in Example 42, the title compound was obtained as amorphous powder by the same procedure as in Example 17.
^{1}H-NMR (DMSO-d_6) δ: 1.04 (3H, d, J = 6.3 Hz), 1.27 (6H, d, J = 6.3 Hz), 1.64 (1H, m), 2.91-3.23 (6H, m), 3.60-3.79 (10H, m), 7.17-7.40 (6H, m), 7.85 (2H, m), 11.0 (1H, m).

Example 166

N-(1-Methyl-3-phenylpropyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-butanamide hydrochloride

[0750]

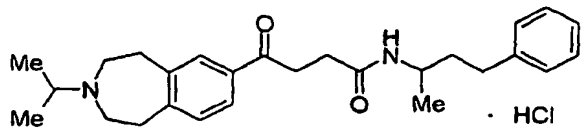


[0751] The title compound was obtained as amorphous powder in the same manner as in Example 36.
^{1}H-NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 6.6 Hz), 1.65 (2H, m) , 2.50-2.60 (6H, m), 3.19 (8H, m), 3.75 (1H, m), 4.37 (1H, m), 7.17-7.40 (6H, m), 7.86-7.96 (2H, m), 9.53 (1H, m).

Example 167

4-(3-Isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-(1-methyl-3-phenylpropyl)-4-oxobutanamide hydrochloride

[0752]

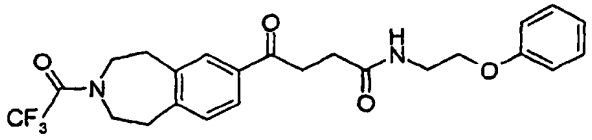


[0753] Using N-(1-methyl-3-phenylpropyl)-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-butanamide hydrochloride obtained in Example 166, the title compound was obtained as amorphous powder by the same procedure as in Example 17.
^{1}H-NMR (DMSO-d_6) δ: 1.05 (3H, d, J = 6.3Hz), 1.27 (6H, d, J = 6.3Hz), 1.67 (2H, m), 2.92-3.23 (6H, m), 3.57-3.79 (5H, m), 3.99-4.05 (5H, m), 7.17-7.40 (6H, m) , 7.86-7.96 (2H, m) , 10.97 (1H, m).

Example 168

4-Oxo-N-(2-phenoxyethyl)-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanamide

[0754]

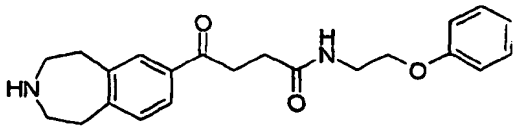


[0755] Using 4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanoic acid obtained in Reference Example 16, the title compound was obtained as powder by the same procedure as in Example 12.
^{1}H-NMR ($CDCl_3$) δ: 2.66 (2H, t, J = 6.6 Hz), 3.03 (4H, m) , 3.34 (2H, t, J = 6.6 Hz), 3.67 (4H, m) , 3.78 (2H, m), 4.04 (1H, d, J = 4.8 Hz), 6.23 (1H, m), 6.89, (3H, m), 7.24(3H, m), 7.78 (2H, m).

Example 169

4-Oxo-N-(2-phenoxyethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide

[0756]

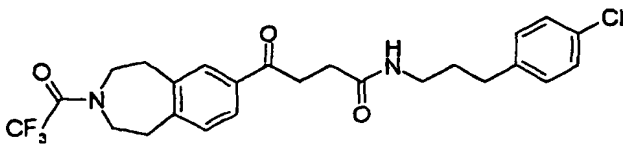


[0757] Using 4-oxo-N-(2-phenoxyethyl)-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanamide obtained in Example 168, the title compound was obtained as powder by the same procedure as in Example 13.
^{1}H-NMR ($CDCl_3$) δ: 2.26 (1H, s), 2.65 (2H, t, J = 6.6 Hz), 2.98 (8H, m), 3.34 (2H, t, J = 6.6 Hz), 3.67 (2H, q, J = 5.1 Hz), 4.04 (2H, t, J = 4.8 Hz), 6.28 (1H, m), 6.89, (3H, m), 7.24(3H, m), 7.71 (2H, m).

Example 170

N-[3-(4-Chlorophenyl)propyl]-4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanamide

[0758]

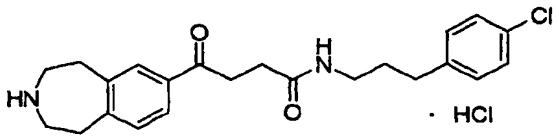


[0759] Using 4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanoic acid obtained in Reference Example 16 and 3-(4-chlorophenyl)propylamine obtained in Reference Example 23, the title compound was obtained as oily matter by the same procedure as in Example 12.
^{1}H-NMR ($CDCl_3$) δ: 1.73-1.85 (2H, m), 2.60 (4H, m) , 3.05 (4H, m), 3.24-3.34 (4H, m), 3.77-3.80 (4H, m), 5.87 (1H, m), 7.09-7.28 (5H, m), 7.77 (2H, m).

Example 171

N-[3-(4-Chlorophenyl)propyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide hydrochloride

[0760]

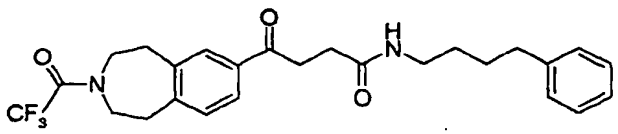


[0761] Using N-[3-(4-chlorophenyl) propyl]-4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanamide obtained in Example 170, the title compound was obtained as amorphous powder by the same procedure as in Example 13.
^{1}H-NMR ($CDCl_3$) δ: 1.73-1.85 (2H, q, J = 7.4 Hz), 2.56-2.72 (6H, m), 2.96 (7H, m), 3.21-3.37 (4H, m), 5.94 (1H, m), 7.07-7.28 (5H, m), 7.75 (2H, m) .

Example 172

4-Oxo-N-(4-phenylbutyl)-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanamide

[0762]

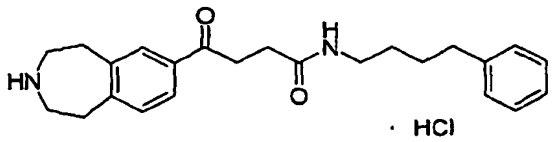


[0763] Using 4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanoic acid obtained in Reference Example 16, the title compound was obtained as oily matter by the same procedure as in Example 12.
^{1}H-NMR ($CDCl_3$) δ: 1.54-1.70 (4H, m) , 2.60 (4H, q, J = 6.6 Hz), 3.05 (4H, m), 3.24-3.34 (4H, m), 3.69-3.81 (4H, m), 5.73 (1H, m), 7.15-7.32 (6H, m), 7.78 (2H, m).

Example 173

4-Oxo-N-(4-phenylbutyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide hydrochloride

[0764]



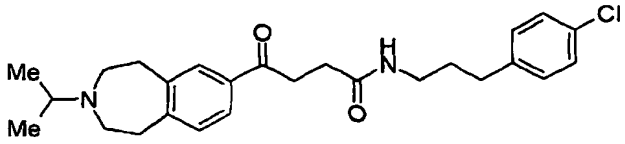
· HCl

[0765] Using 4-oxo-N-(4-phenylbutyl)-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl] obtained in Example 172, the title compound was obtained as amorphous powder by the same procedure as in Example 13.
^{1}H-NMR ($CDCl_3$) δ: 1,54-1.65 (4H, m), 2.48-2.61 (5H, m), 3.01 (8H, m), 3.26-3.49 (4H, m), 5.79 (1H, m), 7.11-7.28 (6H, m), 7.73 (2H, m).

Example 174

N-[3-(4-Chlorophenyl)propyl]-4-oxo-4-(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide

[0766]

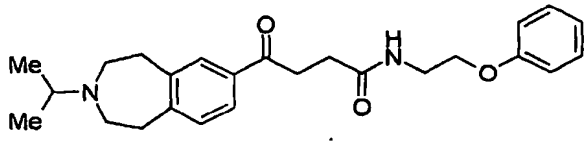


[0767] Using N-[3-(4-chlorophenyl)propyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide hydrochloride obtained in Example 171, the title compound was obtained as powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 1.03 (6H, d , J = 6.6 Hz), 1.77 (2H, m) , 2.57-2.66 (9H, m), 2.96 (4H, m), 3.23-3.34 (4H, m), 5.92 (1H, m), 7.07-7.28 (5H, m), 7.75 (2H, m).

Example 175

4-(3-Isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-N-(2-phenoxyethyl)-butanamide

[0768]

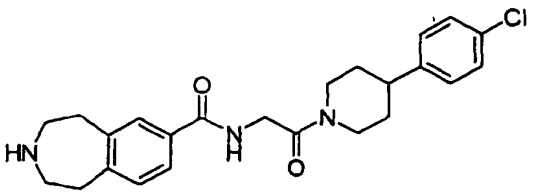


[0769] Using 4-oxo-N-(2-phenoxyethyl)-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide obtained in Example 169, the title compound was obtained as powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 1.02 (6H, d, J = 6.6 Hz), 2.65 (7H, m) , 2.95 (4H, m), 3.34 (2H, t, J = 6.6 Hz), 3.67 (2H, q, J = 5.1 Hz), 4.04 (2H, t, J = 4.8 Hz), 6.23 (1H, m), 6.89, (3H, m), 7.24 (3H, m), 7.71 (2H, m).

Example 176

N-[2-[4-(4-Chlorophenyl)-1-piperidinyl]-2-oxoethyl]-2,3,4,5-tetrahydro-1H-3-benzazepine-7-carboxamide trifluoroacetate

[0770]

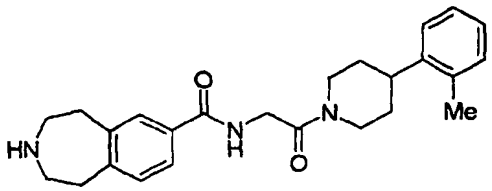


[0771] Using 2-[4-(4-chlorophenyl)-1-piperidinyl]-2-oxoethylamine hydrochloride obtained in Reference Example 22, the title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 426.

Example 177

N-[2-[4-(2-Methylphenyl)-1-piperidinyl]-2-oxoethyl]-2,3,4,5-tetrahydro-1H-3-benzazepine-7-carboxamide trifluoroacetate

[0772]

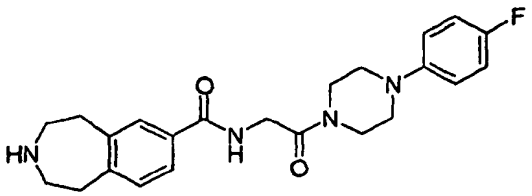


[0773] Using 2-[4-(2-methylpnenyl)-1-piperidinyl]-2-oxoethylamine hydrochloride obtained in Reference Example 23, the title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) : 406.

Example 178

N-[2-[4-(4-Fluorophenyl)-1-piperazinyl]-2-oxoethyl]-2,3,4,5-tetrahydro-1H-3-benzazepine-7-carboxamide trifluoroacetate

[0774]



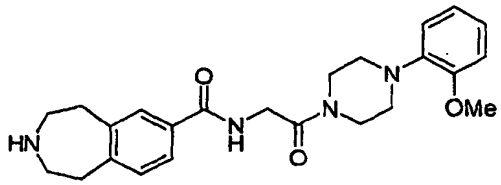
[0775] Using 2-[4-(4-fluorophenyl)-1-piperazinyl]-2-oxoethylamine dihydrochloride obtained in Reference Example 24, the title compound was obtained in the same manner as in Example 36.

MS (APCI) (M+1) : 411.

Example 179

N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]-2-oxoethyl]-2,3,4,5-tetrahydro-1H-3-benzazepine-7-carboxamide trifluoroacetate

[0776]

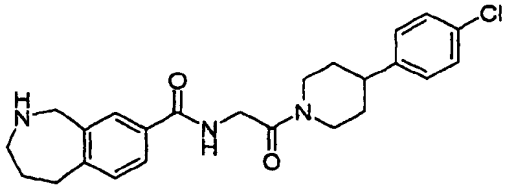


[0777] Using 2-[4-(2-methoxyphenyl)-1-piperazinyl]-2-oxoethylamine dihydrochloride obtained in Reference Example 25, the title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) :423.

Example 180

N-[2-[4-(4-Chlorophenyl)-1-piperidinyl]-2-oxoethyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-8-carboxamide trifluoroacetate

[0778]

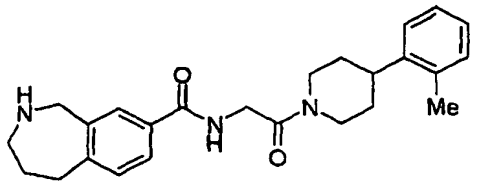


[0779] Using 2-[4-(4-chlorophenyl)-1-piperidinyl]-2-oxoethylamine hydrochloride obtained in Reference Example 22, the title compound was obtained in the same manner as in Example 36.
MS(APCI)(M+1):426.

Example 181

N-[2-[4-(2-Methylphenyl)-1-piperidinyl]-2-oxoethyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-8-carboxamide trifluoroacetate

[0780]

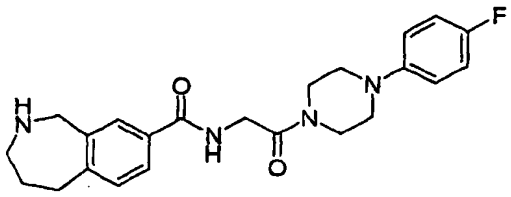


[0781] Using 2-[4-(2-methylphenyl)-1-piperidinyl]-2-oxoethylamine hydrochloride obtained in Reference Example 23, the title compound was obtained in the same manner as in Example 36.
MS(APCI)(M+1):406.

Example 182

N-[2-[4-(4-Fluorophenyl)-1-piperazinyl]-2-oxoethyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-8-carboxamide trifluoroacetate

[0782]

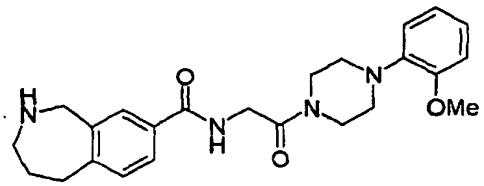


[0783] Using 2-[4-(4-fluorophenyl)-1-piperazinyl]-2-oxoethylamine dihydrochloride obtained in Reference Example 24, the title compound was obtained in the same manner as in Example 36.
MS (APCI) (M+1) :411.

Example 183

N-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]-2-oxoethyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-8-carboxamide trifluoroacetate

[0784]

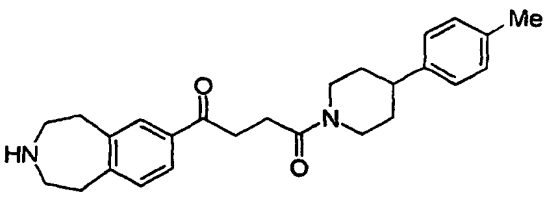


[0785] Using 2-[4-(2-methoxyphenyl)-1-piperazinyl]-2-oxoethylamine dihydrochloride obtained in Reference Example 25, the title compound was obtained by the same procedure as in Example 36.
MS (APCI) (M+1) :423.

Example 184

4-[4-(4-Methylphenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone

[0786]

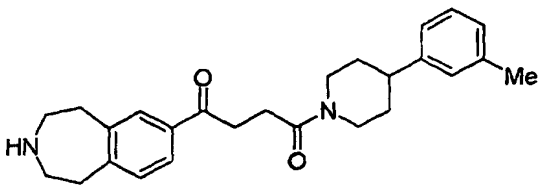


1) Using 4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl]butanoic acid obtained in Reference Example 16, 4-[4-(4-methylphenyl)-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone was obtained as colorless powder by the same procedure as in Example 12.
^{1}H-NMR ($CDCl_3$) δ: 1.55-2.01 (4H, m), 2.33 (3H, s), 2.57-2.91 (4H, m), 2.97-3.27 (5H, m), 3.34 (2H, t, J=6.4Hz), 3.66-3.84 (4H, m), 4.05-4.19 (1H, m), 4.67-4.83 (1H, m), 7.04-7.30 (5H, m), 7.80-7.91 (2H, m).
Melting point: 132-134 °C (crystallizing solvent: diethyl ether)
2) Using 4-[4-(4-methylphenyl)-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone obtained in 1) above, the title compound was obtained as colorless powder by the same procedure as in Example 13.
^{1}H-NMR ($CDCl_3$) δ: 1.47-2.00 (5H, m), 2.33 (3H, s), 2.55-3.04 (12H, m), 3.06-3.26 (1H, m), 3.35 (2H, t, J=6.8Hz), 4.04-4.20 (1H, m), 4.68-4.85 (1H, m), 7.05-7.24 (5H, m), 7.74-7.84 (2H, m).
Melting point: 115-116 °C (crystallizing solvent: diethyl ether)

Example 185

4-[4-(3-Methylphenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone

[0787]

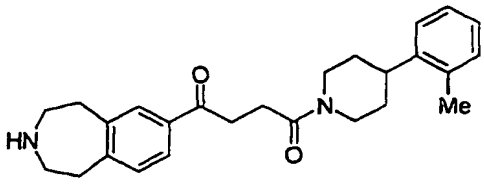


1) Using 4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl]butanoic acid obtained in Reference Example 16, 4-[4-(3-methylphenyl)-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone was obtained as colorless powder by the same procedure as in Example 12.
^{1}H-NMR ($CDCl_3$) δ: 1.55-2.01 (4H, m), 2.35 (3H, s), 2.56-2.93 (4H, m), 2.98-3.27 (5H, m), 3.34 (2H, t, J=6.4Hz), 3.67-3.84 (4H, m), 4.05-4.20 (1H, m), 4.68-4.83 (1H, m), 6.96-7.10 (3H, m), 7.14-7.31 (2H, m), 7.80-7.92 (2H, m).
Melting point: 128-129 °C (crystallizing solvent: diethyl ether)
2) Using 4-[4-(3-methylphenyl)-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone obtained in 1) above, the title compound was obtained as colorless powder by the same procedure as in Example 13.
^{1}H-NMR ($CDCl_3$) δ: 1.45-2.00 (5H, m), 2.34 (3H, s), 2.56-3.03 (12H, m), 3.05-3.26 (1H, m), 3.35 (2H, t, J=6.6Hz), 4.05-4.20 (1H, m), 4.69-4.85 (1H, m), 6.95-7.08 (3H, m), 7.14-7.23 (2H, m), 7.74-7.83 (2H, m).
Melting point: 91-93 °C (crystallizing solvent: diethyl ether)

Example 186

4-[4-(2-Methylphenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone

[0788]



1) Using 4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl]butanoic acid obtained in Reference Example 16, 4-[4-(2-methylphenyl)-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-

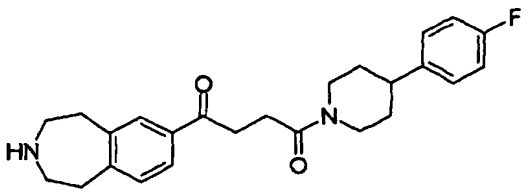
7-yl]-1-butanone was obtained as colorless powder by the same procedure as in Example 12.
^{1}H-NMR ($CDCl_3$) δ: 1.47-1.95 (4H, m), 2.37 (3H, s), 2.58-2.77 (1H, m), 2.80-3.30 (8H, m), 3.35 (2H, t, J=6.6Hz), 3.65-3.85 (4H, m), 4.07-4.23 (1H, m), 4.72-4.87 (1H, m), 7.10-7.32 (5H, m), 7.80-7.92 (2H, m).
Melting point: 145-147 °C (crystallizing solvent: diethyl ether)

2) Using 4-[4-(2-methylphenyl]-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl) -2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone obtained in 1) above, the title compound was obtained as colorless powder by the same procedure as in Example 13.
^{1}H-NMR ($CDCl_3$) δ: 1.50-1.96 (5H, m), 2.37 (3H, s), 2.57-2.76 (1H, m), 2.79-3.28 (12H, m), 3.36 (2H, t, J=6.6Hz), 4.08-4.24 (1H, m), 4.72-4.87 (1H, m), 7.05-7.23 (5H, m), 7.75-7.84 (2H, m).
Melting point: 93-95 °C (crystallizing solvent: diethyl ether)

Example 187

4-[4-(4-Fluorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone

[0789]

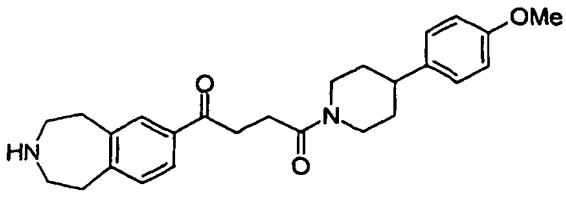


1) Using 4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl]butanoic acid obtained in Reference Example 16, 4-[4-(4-fluorophenyl)-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone was obtained as colorless powder by the same procedure as in Example 12.
^{1}H-NMR ($CDCl_3$) δ: 1.53-2.01 (4H, m), 2.57-2.90 (4H, m), 2.97-3.28 (5H, m), 3.34 (2H, t, J=6.6Hz), 3.65-3.84 (4H, m), 4.05-4.20 (1H, m), 4.68-4.84 (1H, m), 6.95-7.07 (2H, m), 7.10-7.32 (3H, m), 7.80-7.90 (2H, m).
Melting point: 105-102 °C (crystallizing solvent: diethyl ether)
2) Using 4-[4-(4-fluorophenyl)-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone obtained in 1) above, the title compound was obtained as colorless powder by the same procedure as in Example 13.
^{1}H-NMR ($CDCl_3$) δ: 1.47-2.00 (5H, m) , 2.57-2.90 (4H, m) , 2.98 (8H, br), 3.07-3.27 (1H, m), 3.35 (2H, t, J=6.8Hz), 4.06-4.21 (1H, m), 4.70-4.86 (1H, m), 6.94-7.07 (2H, m), 7.10-7.24 (3H, m), 7.74-7.84 (2H, m).
Melting point: 127-128 °C (crystallizing solvent: diethyl ether)

Example 188

4-[4-(4-Methoxyphenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone

[0790]



1) Using 4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl]butanoic acid obtained in Reference Example 16, 4-[4-(2-methylphenyl)-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone was obtained as colorless powder by the same procedure as in Example 12.
^{1}H-NMR ($CDCl_3$) δ: 1.50-1.74 (2H, m), 1.80-1.97 (2H, m), 2.59-2.78 (2H, m), 2.85 (2H, t, J=6.6Hz), 3.00-3.09 (4H,

m), 3.12-3.24 (1H, m), 3.34 (2H, t, J=6.6Hz), 3.67-3.83 (7H, m), 4.07-4.16 (1H, m), 4.71-4.80 (1H, m), 6.86 (2H, d, J=8.6Hz), 7.13 (2H, d, J=8.6Hz), 7.23-7.30 (1H, m), 7.80-7.90 (2H, m). Melting point: 130-131 °C (crystallizing solvent: diethyl ether)

2) Using 4-[4-(2-methylphenyl)-1-piperidinyl]-4-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone obtained in 1) above, the title compound was obtained as colorless powder by the same procedure as in Example 13.

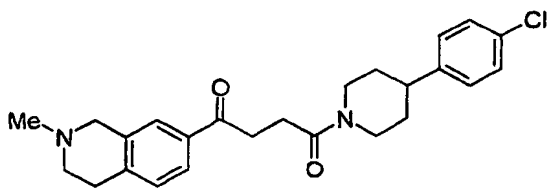
^{1}H-NMR ($CDCl_3$) δ: 1.51-1.97 (5H, m), 2.58-2.77 (2H, m), 2.83 (2H, t, J=6.7Hz), 2.97 (8H, br), 3.10-3.23 (1H, m), 3.35 (2H, t, J=6.7Hz), 3.80 (3H, s), 4.07-4.18 (1H, m), 4.73-4.83 (1H, m), 6.86 (2H, d, J=8.7Hz), 7.13 (2H, d, J=8.7Hz), 7.19 (1H, d, J=8.3Hz), 7.76-7.83 (2H, m).

Melting point: 99-100 °C (crystallizing solvent: diethyl ether)

Example 189

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(2-methyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-oxo-1-butanone

[0791]



[0792] Using 4-[4-(4-chlorophenyl)piperidin-1-yl]-4-oxo-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)butan-1-one obtained in Example 13, the title compound was obtained as colorless powder by the same procedure as in Example 16.

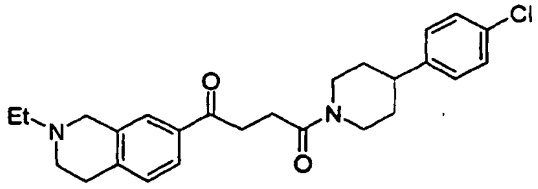
^{1}H-NMR ($CDCl_3$) δ: 1.62 (2H, m), 1.89 (2H, m), 2.48 (3H, s), 2.67-2.70 (4H, m), 2.82 (2H, t, J = 6.4 Hz), 2.97 (2H, t, J = 5.4 Hz), 3.23 (1H, m), 3.34 (2H, t, J = 6.6 Hz), 3.62 (2H, s), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.11-7.31 (5H, m), 7.71-7.81 (2H, m).

Melting point: 139-140 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 190

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(2-ethyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-oxo-1-butanone

[0793]



[0794] Using 4-[4-(4-chlorophenyl)piperidin-1-yl]-4-oxo-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)butan-1-one obtained in Example 13, the title compound was obtained as colorless powder by the same procedure as in Example 17.

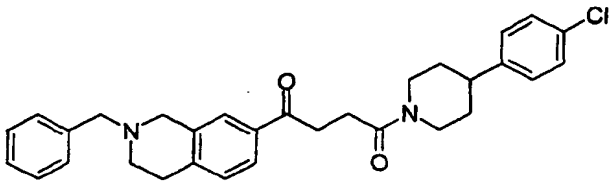
^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, t, J = 7.2 Hz), 1.62 (2H, m), 1.89 (2H, m) , 2.57-2.79 (6H, m), 2.82 (2H, t, J = 6.4 Hz), 2.97 (2H, t, J = 5.4 Hz), 3.23 (1H, m), 3.34 (2H, t, J = 6.6 Hz), 3.62 (2H, s), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.11-7.31 (5H, m), 7.71-7.81 (2H, m).

Melting point: 115-116 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 191

1-(2-Benzyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-butanone

[0795]

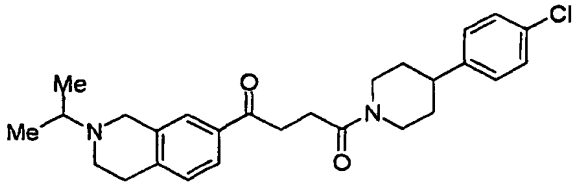


[0796] Using 4-[4-(4-chlorophenyl)piperidin-1-yl]-4-oxo-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)butan-1-one obtained in Example 13, the title compound was obtained as colorless powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 1.62 (2H, m), 1.89 (2H, m), 2.58-2.80 (6H, m), 2.95 (2H, t, J = 5.4 Hz), 3.23 (1H, m), 3.34 (2H, t, J = 6.6 Hz), 3.67 (2H, s), 3.70 (2H, s), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.11-7.41 (10H, m), 7.62-7.80 (2H, m).
Melting point: 102-103 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 192

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(2-isopropyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-oxo-1-butanone

[0797]

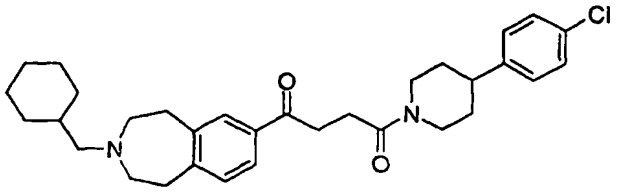


[0798] Using 4-[4-(4-chlorophenyl)piperidin-1-yl]-4-oxo-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)butan-1-one obtained in Example 13, the title compound was obtained as colorless powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 1.15 (6H, d, J = 6.6 Hz), 1.62 (2H, m), 1.89 (2H, m), 2.59-2.95 (9H, m), 3.18 (1H, m), 3.34 (2H, t, J = 6.6 Hz), 3.77 (2H, s), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.11-7.31 (5H, m), 7.73-7.80 (2H, m).
Melting point: 113-115 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 193

4-[4-(4-Chlorophenyl)piperidin-1-yl]-1-(3-cyclohexylmethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxobutan-1-one

[0799]

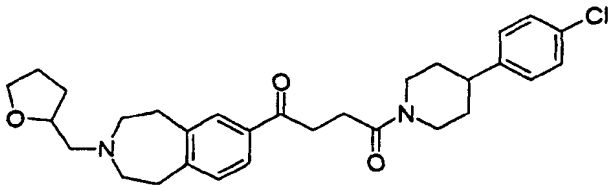


[0800] Using 4-[4-(4-chlorophenyl-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 0.90 (2H, m), 1.24 (4H, m), 1.47-1.94 (10H, m), 2.23 (2H, d, J = 6.9 Hz), 2.58-2.80 (5H, m), 2.94 (2H, t, J = 6.4 Hz), 2.96 (4H, m), 3.23 (1H, m), 3.35 (2H, t, J = 6.6 Hz), 4.13 (1H, m), 4.76 (1H, m), 7.35-7.11 (5H, m), 7.79 (2H, m).
Melting point: 140-141 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 194

4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-[3-(tetrahydro-2-furanylmethyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-butanone

[0801]

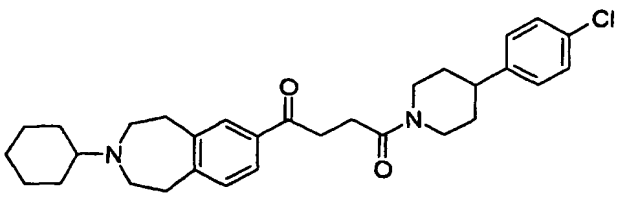


[0802] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17.
MS (ESI) (M+H) : 509.
Melting point: 123-125 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 195

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(3-cyclohexyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-1-butanone

[0803]

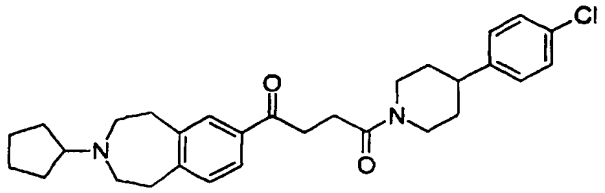


[0804] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17.
MS (ESI) (M+H) : 507.
Melting point: 128-130 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 196

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(3-cyclopentyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-1-butanone

[0805]

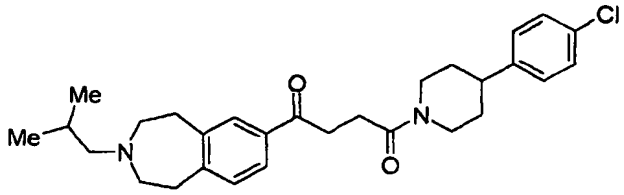


[0806] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 1.55-1.69 (5H, m), 1.83 (3H, m), 2.59-3.03 (17H, m), 3.17 (1H, m), 3.35 (2H, t, J = 6.6 Hz), 4.13 (1H, m), 4.76 (1H, m), 7.35-7.11 (5H, m), 7.79 (2H, m).
Melting point: 160-162 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 197

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(3-isobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-1-butanone

[0807]

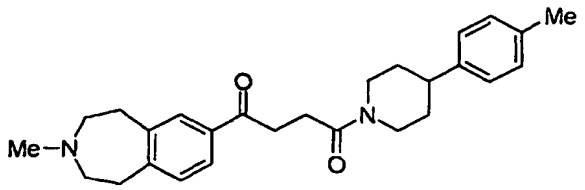


[0808] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 15, the title compound was obtained as colorless powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, d, J = 6.2 Hz), 1.62 (4H, m), 1.89 (3H, m), 2.21 (2H, d, J = 7.4 Hz), 2.60-2.74 (6H, m), 2.79 (2H, t, J = 6.4 Hz), 2.95 (4H, m), 3.23 (1H, m), 3.35 (2H, t, J = 6.6 Hz), 4.13 (1H, m), 4.76 (1H, m), 7.35-7.11 (5H, m), 7.79 (2H, m).
Melting point: 137-138 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 198

4-[4-(4-Methylphenyl)-1-piperidinyl]-1-(3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-1-butanone

[0809]



[0810] Using 4-[4-(4-methylphenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 184, the title compound was obtained as colorless powder by the same procedure as in Example 16.

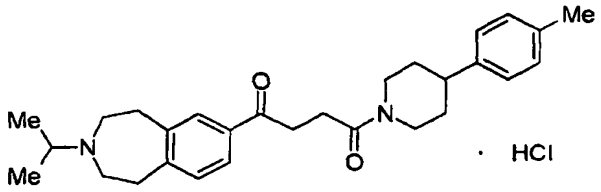
^{1}H-NMR ($CDCl_3$) δ: 1.66 (2H, m) , 1.89 (2H, m) , 2.33 (3H, s), 2.38 (3H, s), 2.65 (6H, m), 2.82 (2H, t, J = 6.4 Hz), 2.95 (4H, m) , 3.23 (1H, m), 3.35 (2H, t, J = 6.6 Hz), 4.13 (1H, m), 4.76 (1H, m), 7.35-7.11 (5H, m), 7.79 (2H, m).

Melting point: 111-112 °C (crystallizing solvent: ethancl-diisopropyl ether)

Example 199

1-(3-Isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-methylphenyl)-1-piperidyl]-4-oxo-1-butanone hydrochloride

[0811]



[0812] Using 4-[4-(4-methylphenyl)-1-piperidinyl]-4-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone obtained in Example 184, the title compound was obtained as colorless powder by the same procedure as in Example 17.

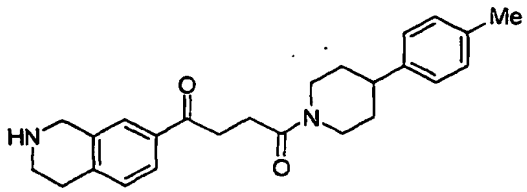
^{1}H-NMR ($CDCl_3$) δ: 1.26 (7H, m), 1.56 (1H, m) , 1.78 (2H, m) , 2.26 (3H, s), 2.50 (1H, m), 2.73 (2H, m), 2.94-3.64 (7H, m), 4.05 (1H, m), 4.46 (1H, m), 7.12 (4H, s), 7.40 (1H. d, J = 8.4 Hz), 7.83 (2H, m).

Melting point: 180 °C (decomp.) (crystallizing solvent: ethanol-diisopropyl ether)

Example 200

4-[4-(4-Methylphenyl)piperidin-1-yl]-4-oxo-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)butan-1-one

[0813]

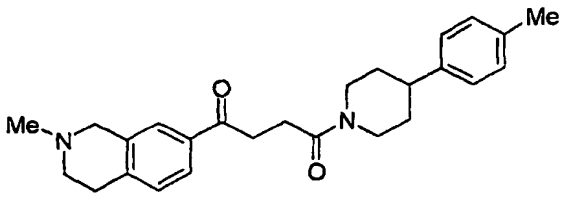


[0814] Using 4-oxo-4-[2-(trifluoroacetyl)-1,2,3,4-tetrahydro-7-isoquinolinyl]butanoic acid obtained in Reference Example 15, the title compound was obtained as colorless powder by the same procedures as in Examples 12 and 13.
^{1}H-NMR ($CDCl_3$) δ: 1.63 (2H, m), 1.95 (3H, m), 2.33 (3H, s), 2.59-2.72 (3H, m), 2.82 (4H, m), 2.97 (2H, t, J = 5.4 Hz), 3.17 (2H, t, J = 6.2 Hz), 3.34 (2H, t, J = 6.6 Hz), 4.08 (2H, s), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.11-7.20 (5H, m), 7.71-7.81 (2H, m).
Melting point: 119-120 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 201

4-[4-(4-Methylphenyl)-1-piperidinyl]-1-(2-methyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-oxo-1-butanone

[0815]

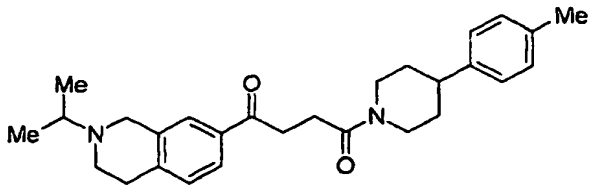


[0816] Using 4-[4-(4-methylphenyl) piperidin-1-yl]-4-oxo-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)butan-1-one obtained in Example 200, the title compound was obtained as colorless powder by the same procedure as in Example 16.
^{1}H-NMR ($CDCl_3$) δ: 1.62 (2H, m) , 1.89 (2H, m) , 2.34 (3H, s), 2.48 (3H, s), 2.60-2.73 (4H, m), 2.82 (2H, t, J = 6.4 Hz), 2.97 (2H, t, J = 5.4 Hz), 3.23 (1H, m), 3.34 (2H, t, J = 6.6 Hz), 3.62 (2H, s), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.11-7.31 (5H, m), 7.71-7.81 (2H, m).
Melting point: 97-99 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 202

1-(2-Isopropyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-[4-(4-methylphenyl)-1-piperidinyl]-4-oxo-1-butanone

[0817]

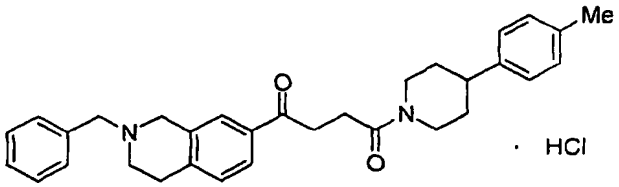


[0818] Using 4-[4-(4-methylphenyl)piperidin-1-yl]-4-oxo-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)butan-1-one obtained in Example 200, the title compound was obtained as colorless powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 1.15 (6H, d, J = 6.6 Hz), 1.62 (2H, m), 1.89 (2H, m), 2.64 (3H, s), 2.65-2.95 (9H, m), 3.18 (1H, m), 3.34 (2H, t, J = 6.6 Hz), 3.77 (2H, s), 4.13 (1H, d, J = 15.6 Hz), 4.76 (1H, d, J = 12 Hz), 7.11-7.31 (5H, m), 7.73-7.80 (2H, m).
Melting point: 78-80 °C (crystallizing solvent: ethanol-diisopropyl ether)

Example 203

1-(2-Benzyl-1,2,3,4-tetrahydro-7-isoquinolinyl)-4-[4-(4-methylphenyl)-1-piperidinyl]-4-oxo-1-butanone hydrochloride

[0819]

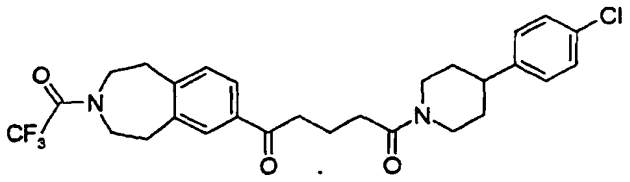


[0820] Using 4-[4-(4-methylphenyl)piperidin-1-yl]-4-oxo-1-(1,2,3,4-tetrahydroisoquinolin-7-yl)butan-1-one obtained in Example 200, the title compound was obtained as colorless powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 1.36 (1H, m) , 1.56 (1H, m), 1.78 (2H, m), 2.26 (3H, s), 2.50 (1H, m), 2.73 (2H, m), 3.08-3.43 (8H, m), 3.67 (1H, m), 4.05 (1H, m), 4.46 (4H, m), 7.12 (4H, s), 7.41 (1H. d, J = 8.4 Hz), 7.53 (3H, m), 7.67 (2H, m), 7.86 (2H, m).
Melting point: 72 °C (decomp) (crystallizing solvent: ethanol-diisopropyl ether)

Example 204

5-[4-(4-Chlorophenyl)-1-piperidinyl]-5-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-pentanone

[0821]

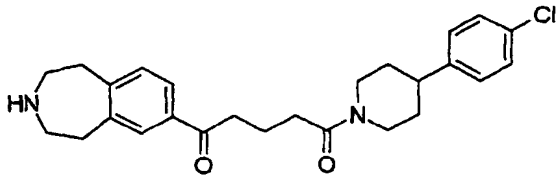


[0822] Using 2,3,4,5-tetrahydro-1H-3-benzazepine, the title compound was obtained as colorless amorphous powder by the same procedures as in Reference Example 15 and in Example 12.
^{1}H NMR ($CDCl_3$) δ: 1.57 (2H, m), 1.89 (2H, m), 2.10 (2H, m) , 2.49 (2H, m), 2.58-2.76 (2H, m), 3.01-3.17 (7H, m), 3.75 (4H, m), 4.04 (1H, m), 4.79 (1H, m), 7.11 (2H, m), 7.28 (3H, m), 7.82 (2H, m).

Example 205

5-[4-(4-Chlorophenyl)-1-piperidinyl]-5-oxo-1-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-pentanone

[0823]

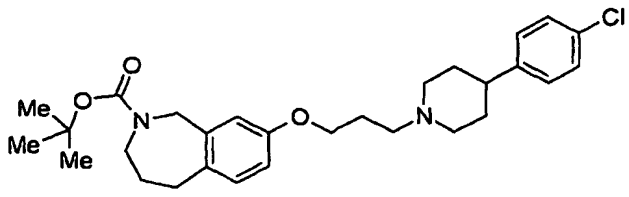


[0824] Using 5-[4-(4-chlorophenyl)-1-piperidinyl]-5-oxo-1-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]-1-pentanone obtained in Example 204, the title compound was obtained as colorless powder by the same procedure as in Example 13.
^{1}H NMR ($CDCl_3$) δ: 1.57 (2H, m), 1.87 (2H, m), 2.10 (2H, m), 2.48 (2H, m), 2.58-2.75 (2H, m), 2.96 (8H, m), 3.10 (3H, m), 4.04 (1H, m), 4.79 (1H, m), 7.11 (2H, m), 7.18 (1H, m), 7.28 (2H, m), 7.73 (2H, m).
FABMS (pos) 439 $[M+H]^+$.
Melting point: 112-113 °C (crystallizing solvent: ethyl acetate-diisopropyl ether)

Example 206

tert-Butyl 8-[3-[4-(4-chlorophenyl)-1-piperidinyl] propoxy]-1,3,4,5-tetrahydro-2 H-2-benzazepine-2-carboxylate

[0825]

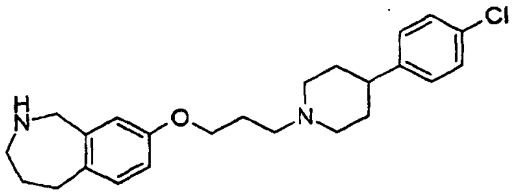


[0826] A solution of tert-butyl 8-hydroxy-1,3,4,5-tetrahydro-2 H-2-benzazepine-2-carboxylate (1.00 g, 3.80 mmol) obtained in Reference Example 27, 3-bromo-1-chloropropane (0.451 ml, 4.56 mmol) and potassium carbonate (2.62 g, 19.0 mmol) in dimethylformamide (10 ml) was stirred at 80 °C for 3 hours. Ethyl acetate was added to the resultant solution which was then washed with a saturated saline solution and dried over anhydrous sodium sulfate. After the solvent was concentrated under reduced pressure, the resultant residues were purified by alumina column chromatography (developing solvent; ethyl acetate). The resultant oily matter and a solution of 4-(4-chlorophenyl) piperidine (882 mg, 3.80 mmol), potassium carbonate (2.62 g, 19.0 mmol) and sodium iodide (569 mg, 3.80 mmol) in dimethylformamide (10 ml) were stirred at 80 °C for 3 hours. Ethyl acetate was added to the resultant solution which was then washed with a saturated saline solution and dried over anhydrous sodium sulfate. After the solvent was concentrated under reduced pressure, the resultant residues were purified by silica gel column chromatography (developing solvent; hexane : ethyl acetate = 3 : 1), whereby the title compound (1.25 g) was obtained.
^{1}H NMR ($CDCl_3$) δ: 1.41 (9H, s), 1.72-1.82 (6H, m), 1.96-2.05 (4H, m), 2.48-2.58 (3H, m), 2.88 (2H, m), 3.03-3.09 (2H, m), 3.66 (2H, m), 4.01 (2H, m), 4.32-4.39 (2H, m), 6.66-6.75 (2H, m), 7.01-7.05 (1H, m), 7.15 (2H, d, J = 8.6 Hz), 7.26 (2H, d, J = 8.6 Hz).

Example 207

8-[3-[4-(4-Chlorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1 H-2-benzazepine

[0827]

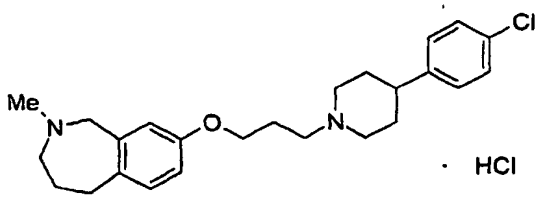


[0828] A solution of tert-butyl 8-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-1,3,4,5-tetrahydro-2H-2-benzazepine-2-carboxylate (1.10 g, 2.20 mmol) obtained in Example 206 in trifluoroacetic acid (10 ml) was stirred for 1 hour and then concentrated under reduced pressure. Ethyl acetate was added to the resultant oily matter which was then washed with an aqueous potassium carbonate solution and a saturated saline solution and dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure, and the resultant residues were formed into powder with hexane, to give the title compound (682 mg).
^{1}H NMR (DMSO-d_6) δ: 1.57-2.03 (10H, m), 2.43 (3H, m), 2.78 (2H, m), 3.00 (4H, m), 3.72 (2H, m), 3.96 (2H, m), 6.55-6.70 (2H, m), 7.02 (1H, d, J = 8.0 Hz), 7.24-7.36 (4H, m).
Melting point: 97-99 °C (crystallizing solvent: diisopropyl ether-hexane)

Example 208

8-[3-[4-(4-Chlorophenyl)-1-piperidinyl]propoxy]-2-methyl-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride

[0829]



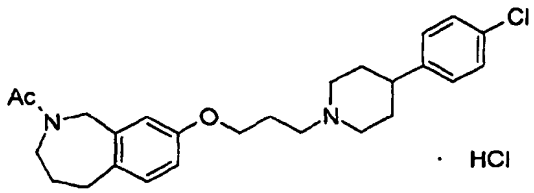
[0830] Using 8-[3-[4-(4-chlorophenyl)-1-piperidinyl] propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine obtained in Example 207, the title compound was obtained as colorless amorphous powder by the same procedure as in Example 16.
^{1}H NMR ($CDCl_3$, free base) δ: 1.71-1.80 (6H, m), 1.96-2.07 (4H, m), 2.31 (3H, s), 2.45-2.57 (3H, m), 2.81 (2H, m),

2.98-3.09 (4H, m), 3.75 (2H, s), 3.99 (2H, t, J = 6.3 Hz), 6.65-6.71 (2H, m), 7.01 (1H, d, J = 7.2 Hz), 7.15 (2H, d, J = 8.7 Hz), 7.26 (2H, d, J = 8.7 Hz).

Example 209

2-Acetyl-8-[3-[4-(4-chlorophenyl)-1-piperidinyl]propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine hydrochloride

[0831]

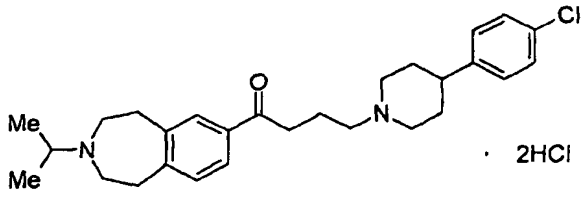


[0832] Using 8-[3-[4-(4-chlorophenyl)-1-piperidinyl] propoxy]-2,3,4,5-tetrahydro-1H-2-benzazepine obtained in Example 207 and acetic anhydride, the title compound was obtained as colorless amorphous powder by the same procedure as in Example 17.
^{1}H NMR (DMSO-d_6) δ: 1.84 (2H, m), 2.01 (2H, m), 2.32 (3H, s), 2.47-2.62 (4H, m), 2.75-2.95 (5H, m), 3.24 (2H, m), 3.70-3.82 (4H, m), 4.09 (2H, m), 4.57 (2H, m), 6.72-6.90 (2H, m), 7.09 (1H, m), 7.21-7.30 (4H, m).

Example 210

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-butanone dihydrochloride

[0833]

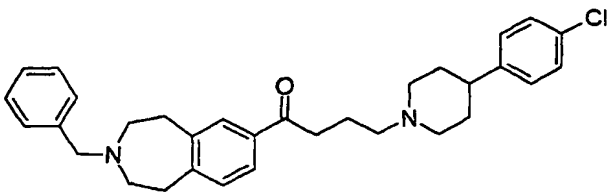


[0834] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl)-1-butanone obtained in Example 34, the title compound was obtained as colorless powder by the same procedure as in Example 17.
1H-NMR ($CDCl_3$) δ:1.02 (6H, d, J = 6.6Hz), 1.62-1.74 (6H, m) , 1.93-2.05 (4H, m), 2.44 (2H, t like), 2.63-2.67 (2H, m), 2.89-3.05 (10H, m), 7.09-7.27 (5H, m), 7.72-7.75 (2H, m).
Melting point: 236 °C (decomp) (crystallizing solvent: ethyl acetate-hexane)

Example 211

1-(3-Benzyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-1-butanone

[0835]

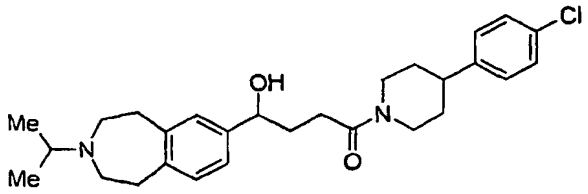


[0836] Using 4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl)-1-butanone obtained in Example 34, the title compound was obtained as colorless powder by the same procedure as in Example 17.
^{1}H-NMR ($CDCl_3$) δ: 1.60-1.79 (6H, m), 1.96-2.08 (4H, m), 2.43 (2H, t like), 2.61-2.65 (2H, m), 2.94-3.04 (9H, m), 3.63 (2H, s), 7.09-7.36 (10H, m), 7.71-7.75 (2H, m).
Melting point: 99-100 °C (crystallizing solvent: ethyl acetate-hexane)

Example 212

4-[4-(4-Chlorophenyl)-1-piperidinyl]-1-(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-1-butanol

[0837]

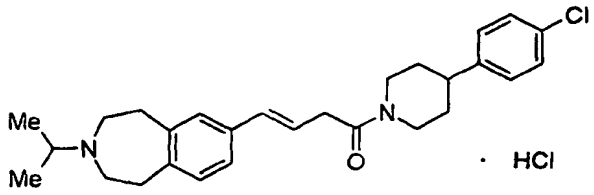


[0838] Sodium borohydride (81 mg, 2.14 mmol) was added to a suspension of 4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-1-butanone (0.50 g, 1.07 mmol) obtained in Example 30 in methanol (20 mL), and the mixture was stirred at room temperature for 30 minutes. The reaction solution was concentrated under reduced pressure, and the residues were partitioned into ethyl acetate and water. The ethyl acetate layer was washed with a saturated saline solution and dried over magnesium sulfate. The solvent was distilled away under reduced pressure, whereby the title compound was obtained as amorphous powder.
1H-NMR ($CDCl_3$) δ: 1.02 (6H, d, J = 6.6Hz), 1.54-1.63 (2H, m), 1.85-1.91 (2H, br m), 2.05-2.17 (2H, m), 2.54 (2H, t like), 2.66-2.78 (6H, m), 2.89-2.93 (5H, m), 3.12 (1H, m), 3.95 (1H, br d), 4.72-4.85 (2H, m), 7.04-7.14 (5H, m), 7.30-7.31 (2H, m).

Example 213

7-[(E)-4-[4-(4-Chlorophenyl)-1-piperidinyl]-4-oxo-1-butenyl]-3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride

[0839]

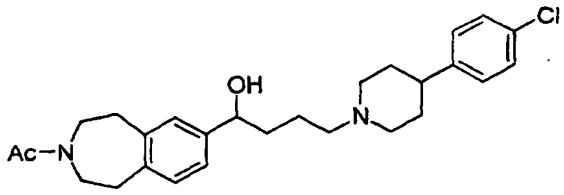


[0840] A solution of 4-[4-(4-chlorophenyl)-1-piperidinyl]-1-(3-isopropyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-oxo-1-butanol (0.14 g, 0.30 mmol) obtained in Example 212 and p-toluenesulfonic acid monohydrate (0.03 g, 0.16 mmol) in toluene (10 mL) was refluxed for 24 hours under heating. The reaction solution was concentrated under reduced pressure, and the resultant residues were purified by alumina column chromatography (developing solvent; hexane : ethyl acetate = 1 : 1), whereby 0.09 g free base of the title compound was obtained as colorless amorphous powder. The resultant powder was dissolved in ethyl acetate and treated with 4 N hydrochloric acid in ethyl acetate under cooling with ice-bath, whereby 0.04 g of the title compound was obtained as colorless amorphous powder.
1H-NMR ($CDCl_3$) δ: 1.02 (6H, d, J = 6.6Hz), 1.50-1.71 (2H, m), 1.86-1.92 (2H, m), 2.57-2.72 (6H, m), 2.87-3.00 (5H, m), 2.64 (1H, m), 3.34 (2H, d, J = 6.2Hz), 4.01-4.07 (1H, br d like), 4.78-4.85 (1H, br d like), 6.26-6.37 (1H, m), 6.46 (1H, d, J = 16.2Hz), 7.05-7.29 (7H, m).

Example 214

1-(3-Acetyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-1-butanol

[0841]

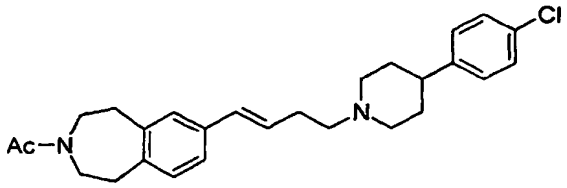


[0842] Using 1-(3-acetyl-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-1-butanone obtained in Example 33, the title compound was obtained as colorless powder by the same procedure as in Example 212.
1H-NMR ($CDCl_3$) δ: 1.50-2.27 (14H, m), 2.42-2.60 (3H, m) , 2.85-2.97 (4H, m), 3.01-3.10 (1H, m), 3.23-3.32 (1H, m), 3.47-3.82 (4H, m), 4.64 (1H, brd, J = 5.4Hz), 7.05-7.30 (7H, m) .
Melting point: 113-114 °C (crystallizing solvent: diethyl ether)

Example 215

3-Acetyl-7-[(E)-4-[4-(4-chlorophenyl)-1-piperidinyl]-1-butenyl]-2,3,4,5-tetrahydro-1H-3-benzazepine

[0843]



[0844] Using 1-(3-acetyl-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl)-4-[4-(4-chlorophenyl)-1-piperidinyl]-1-butanol obtained in Example 214, the title compound was obtained as colorless powder by the same procedure as in Example 213.

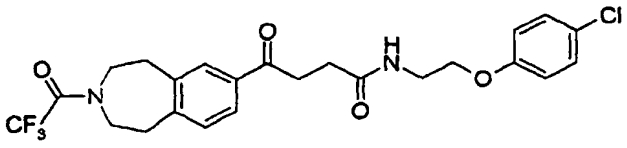
^{1}H-NMR ($CDCl_3$) δ: 1.57-1.90 (4H, m), 2.04-2.17 (2H, m), 2.19 (3H, s), 2.39-2.58 (5H, m), 2.84-2.95 (4H, m), 3.05-3.15 (2H, m), 3.52-3.61 (2H, m), 3.68-3.77 (2H, m), 6.13-6.27 (1H, m), 6.39 (1H, d, J = 15.7Hz), 7.03-7.20 (5H, m), 7.23-7.30 (2H, m) .

Melting point: 153-155 °C (crystallizing solvent: diethyl ether)

Example 216

N-[2-(4-Chlorophenoxy)ethyl]-4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanamide

[0845]



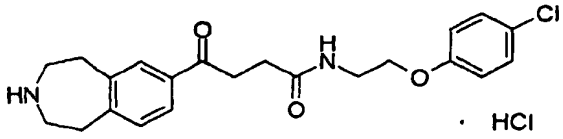
[0846] Using 4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl]butanoic acid obtained in Reference Example 16 and 2-(4-chlorophenoxy)ethylamine obtained in Reference Example 26, the title compound was obtained as oily matter by the same procedure as in Example 12.

^{1}H-NMR ($CDCl_3$) δ: 2.65 (2H, t, J = 6.6 Hz), 3.02 (4H, m), 3.32 (2H, t, J = 6.6 Hz), 3.62-3.69 (4H, m), 3.78 (2H, m), 3.97 (2H, t, J = 5.4 Hz), 6.24 (1H, m), 6.81 (2H, m), 7.22-7.28 (3H, m), 7.78 (2H, m).

Example 217

N-[2-(4-Chlorophenoxyl)ethyl]-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl]butanamide hydrochloride

[0847]



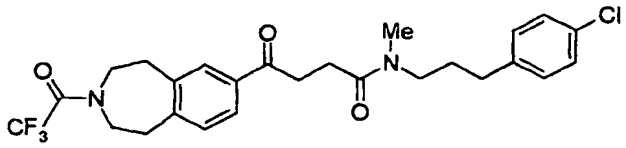
[0848] Using N-[2-(4-chlorophenoxy)ethyl]-4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl] butanamide obtained in Example 216, the title compound was obtained as amorphous powder by the same procedure

as in Example 13.
^{1}H-NMR ($CDCl_3$, free base) δ: 2.02 (1H, m) , 2.65 (2H, t, J = 6.6 Hz), 2.99 (8H, m), 3.33 (2H, t, J = 6.6 Hz), 3.66 (2H, m), 3.97 (2H, t, J = 5.4 Hz), 6.31 (1H, m), 6.81 (2H, m), 7.16-7.27 (3H, m), 7.70 (2H, m).

Example 218

N-[3-(4-Chlorophenyl)propyl]-N-methyl-4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl] butanamide

[0849]

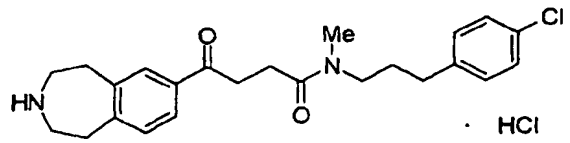


[0850] 3-(4-Chlorophenyl)propylamine (1.69 g, 9.96 mmol) and 37 % aqueous formaldehyde (0.811 ml, 10.0 mmol) was stirred at 100 °C for 7 hours in formic acid (10 ml). The resultant mixture was cooled to room temperature, and the formic acid was distilled away, and the reaction solution was made basic with 8 N aqueous sodium hydroxide and extracted with ethyl acetate. The extract was washed with an aqueous saturated NaCl solution and dried over anhydrous magnesium sulfate. The solvent was distilled away under reduced pressure, and the resultant residues, 4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1H-3-benzazepin-8-yl]butanoic acid (3.4 g, 9.96 mmol) obtained in Reference Example 16, and triethylamine (1.39 ml, 9.96 mmol) were stirred in dimethylformamide (5 ml) at room temperature for 30 minutes and then cooled to 0 °C, followed by adding diethyl cyanophosphate (1.51 ml, 9.96 mmol). The resultant mixture was stirred for 1 hour, poured into water and extracted with ethyl acetate. The extract was washed with an aqueous saturated NaCl solution and dried over anhydrous magnesium sulfate. After the solvent was distilled away under reduced pressure, the residues were purified by silica gel column chromatography (developing solvent; ethyl acetate : hexane : 1 : 1), whereby 1.44 g of the title compound was obtained as oily matter.
^{1}H-NMR ($CDCl_3$) δ: 1.86 (2H, m) , 2.57-2.80 (4H, m) , 3.05 (7H, m), 3.30-3.36 (4H, m), 3.77-3.79 (4H, m), 7.10-7.33 (5H, m), 7.76 (2H, m).

Example 219

N-[3-(4-Chlorophenyl)propyl]-N-methyl-4-oxo-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)butanamide hydrochloride

[0851]

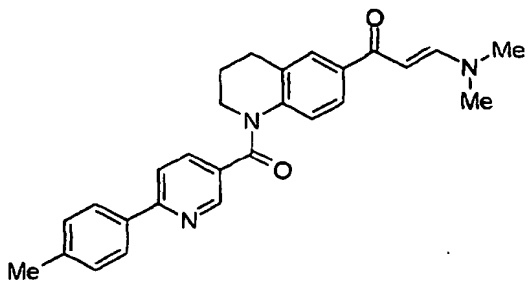


[0852] Using N-[3-(4-chlorophenyl) propyl]-N-methyl-4-oxo-4-[3-(trifluoroacetyl)-2,3,4,5-tetrahydro-1 H-3-benzazepin-7-yl]butanamide obtained in Example 218, the title compound was obtained as amorphous powder by the same procedure as in Example 13.
^{1}H-NMR ($CDCl_3$, free base) δ: 1.76-2.05 (3H, m), 2.51-2.68 (6H, m), 3.00 (7H, m), 3.24-3.41 (4H, m), 3.90 (2H, m), 7.07-7.30 (5H, m), 7.76 (2H, m) .

Example 220

(E)-3-(Dimethylamino)-1-[1-[[6-(4-methylphenyl)-3-pyridinyl]carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-2-propen-1-one

[0853]

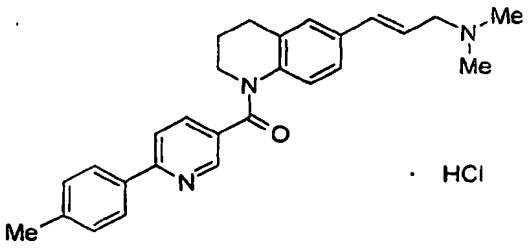


1) Using 6-acetyl-1,2,3,4-tetrahydroquinoline and 6-(4-methylphenyl)nicotinic acid, 1-[1-[[6-(4-methylphenyl)-3-pyridinyl]carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]ethanone was obtained as pale yellow powder by the same procedure as in Reference Example 5.
^{1}H-NMR (DMSO-d_6) δ: 2.00 (2H, m), 2.36 (3H, s), 2.49 (3H, s), 2.93 (2H, dd, J=6.3 and 6.6Hz), 3.83 (2H, dd, J=6.1 and 6.3Hz), 7.00 (1H, d, J=9.3Hz), 7.30 (2H, d, J=8.1Hz), 7.52 (1H, dd, J=1.5 and 8.3Hz), 7.83 (2H, m), 7.95 (1H, d, J=8.3Hz), 8.01 (2H, d, J=8.1Hz), 8.59 (1H, m).
2) Using 1-[1-[[6-(4-methylphenyl)-3-pyridinyl] carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]ethanone obtained in 1) above, the title compound was obtained as pale yellow powder by the same procedure as in Reference Example 6.
^{1}H-NMR (DMSO-d_6) δ: 2.00 (2H, tt, J=6.3, 6.3Hz), 2.35 (3H, s), 2.87 (3H, br s), 2.91 (2H, t, J=6.3Hz), 3.11 (3H, br s), 3.83 (2H, t, J=6.3Hz), 5.78 (1H, d, J=12.5Hz), 6.86 (1H, d, J=8.1Hz), 7.30 (2H, d, J=8.3Hz), 7.66 (1H, d, J=12.5Hz), 7.80 (3H, m), 7.94 (1H, d, J=8.3Hz), 8.00 (2H, d, J=8.1Hz), 8.57 (1H, m).

Example 221

(E)-N,N-Dimethyl-3-[1-[[6-(4-methylphenyl)-3-pyridinyl]carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-2-propene-1-amine hydrochloride

[0854]

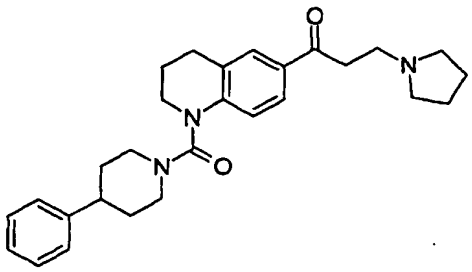


[0855] Using (E)-3-(dimethylamino)-1-[1-[[6-(4-methylphenyl)-3-pyridinyl]carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-2-propen-1-one obtained in Example 220, the title compound was obtained as yellow crystals by the same procedures as in Examples 4 and 5.
^{1}H-NMR (DMSO-d_6) δ: 1.98 (2H, m), 2.36 (3H, s), 2.70 (3H, s), 2.71 (3H, s), 2.86 (2H, t, J=6.3Hz), 3.00 (2H, m), 3.79 (2H, t, J= 6.3Hz), 5.66 (1H, m), 6.98 (2H, s), 7.24 (1H, s), 7.31 (2H, d, J=8.1Hz), 7.86 (1H, m), 7.96 (1H, m), 8.00 (2H, d, J=8.1Hz), 8.57 (1H, m), 10.42 (1H, br s).

Example 222

1-[1-[(4-Phenyl-1-piperidinyl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-3-(1-pyrrolidinyl)-1-propanone

[0856]

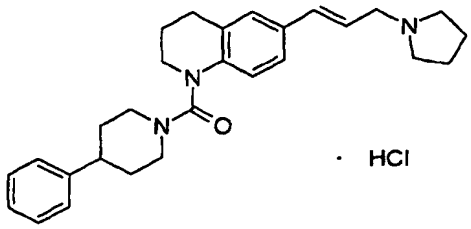


[0857] Using 1-[(4-phenyl-1-piperidinyl)carbonyl]-1,2,3,4-tetrahydroquinoline obtained in Reference Example 28, the title compound was obtained as colorless solution by the same procedures as in Reference Examples 7 and 8.
^{1}H-NMR ($CDCl_3$) δ: 1.70 (2H; m) , 1.79 (4H, m) , 1.84 (2H, m) , 2.01 (2H, m), 2.56 (4H, m), 2.69 (1H, m), 2.84 (2H, t, J=6.6Hz), 2.89 (2H, dd, J=7.0 and 8.0Hz), 2.91 (2H, m), 3.14 (2H, dd, J=7.0 and 8.0Hz), 3.64 (2H, t, J=5.8Hz), 4.05 (2H, m), 7.02 (1H, d, J=8.8Hz), 7.19-7.33 (5H, m), 7.73 (2H, m) .

Example 223

1-[(4-Phenyl-1-piperidinyl)carbonyl]-6-[(E)-3-(1-pyrrolidinyl)-1-propenyl]-1,2,3,4-tetrahydroquinoline hydrochloride

[0858]



[0859] Using 1-[1-[(4-phenyl-1-piperidinyl)carbonyl]-1,2,3,4-tetrahydro-6-quinolinyl]-3-(1-pyrrolidinyl)-1-propanone obtained in Example 222, the title compound was obtained as yellow amorphous powder by the same procedures as in Examples 4 and 5.
^{1}H-NMR (DMSO-d_6) δ: 1.70 (2H, m), 1.83 (2H, m), 1.97 (2H, m), 2.07 (2H, m), 2.23 (2H, m), 2.68 (1H, m), 2.79 (2H, m), 2.88 (4H, m), 3.64 (2H, m), 3.72 (2H, m), 3.78 (2H, m), 4.00 (2H, m), 6.32 (1H, m), 6.82 (1H, d, J=15.8Hz), 7.14-7.33 (8H, m), 12.54 (1H, br s).

Preparation Example 1

[0860]

(1) Compound obtained in Example 1	50 mg
(2) Lactose	34 mg
(3) Corn starch	10.6 mg
(4) Corn starch (paste)	5 mg
(5) Magnesium stearate	0.4 mg

(continued)

(6) Carboxymethylcellulose calcium	20 mg
Total	120 mg

[0861] In accordance with a conventional manner, the above (1) to (6) are admixed and tableted using a tableting machine to give tablets.

Preparation Example 2

[0862]

(1) Compound obtained in Example 5	50 mg
(2) Lactose	34 mg
(3) Corn starch	10.6 mg
(4) Corn starch (paste)	5 mg
(5) Magnesium stearate	0.4 mg
(6) Carboxymethylcellulose calcium	20 mg
Total	120 mg

[0863] In accordance with a conventional manner, the above (1) to (6) are admixed and tableted using a tableting machine to give tablets.

Reference Example 1-1

Amplification of rat SLC-1 receptor cDNA by PCR method using rat-brain-originated cDNA

[0864] Reverse transcription reaction was carried out using random primer, with rat-brain-originated poly (A)$^+$RNA (Clone Tech Co.) as a template. The reagent from the TaKaRa RNA PCR ver. 2 kit was used for the reverse transcription reaction. Next, using this reverse transcription product as a template, amplification was carried out by a PCR method using synthetic DNA primers with SEQ ID NOS: 1 and 2. Synthetic DNA primers were constructed to amplify genes in the domain where genes were translated into the receptor protein. At that time, individual restriction enzyme recognition sequences were also added to the 5' side and 3' side of the gene so as to add a nucleotide sequence recognizing the restriction enzyme Sal I to the 5' side of the gene, and to add a nucleotide sequence recognizing the restriction enzyme Spe I to the 3' side of the gene. The reaction mixture was composed of 5 μl of cDNA template, 0.4 μM of synthetic DNA primer, 0.25 mM of dNTPs, 0.5 μl of Pfu (StrataGene Co.) DNA polymerase, and buffers attached to enzymes, with setting total reaction quantity at 50 μl.

[0865] A thermal cycler (Parkin Elmer Co.) was used to produce cycles for amplification. After heating at 94°C for 60 seconds, the cycle consisting of 94°C for 60 seconds, 60°C for 30 seconds, and 72°C for 150 seconds, was repeated 35 times, and finally reaction was conducted at 72°C for 10 minutes. After 0.8% agarose gel electrophoresis, the amplified products were confirmed by ethidium bromide dying. Reference Example 1-2 Subcloning of PCR products into plasmid vector, and confirmation of an amplified cDNA sequence by decoding of a nucleotide sequence in an inserted cDNA portion

[0866] The reaction product after PCR conducted in Reference Example 1-1 was separated using 0.8% low-melting point agarose gel. After the band section was cut out using a razor, DNA was recovered by conducting fragmentation, phenol extraction, phenol-chloroform extraction and ethanol precipitation. The recovered DNA was subcloned on plasmid vector PCR-Script Amp SK(+) in accordance with prescription of the PCR-Script™ Amp SK(+) cloning kit (Stratagene Co.). After this was introduced into Escherichia coli XL-1 Blue (Stratagene Co.) by transformation, the clones with fragments of inserted cDNA were selected in LB agar culture medium containing ampicillin and X-gal. Only clones showing white color were separated using a sterilized toothpick, and transformant E. coli XL-1 Blue/rat SLC-1 was obtained.

[0867] Each clone was cultured overnight in LB culture medium containing ampicillin, and plasmid DNA was prepared using QIA prep8 mini prep (Qiagen). A portion of the prepared DNA was digested with Sal I and Spe I, and the size of the inserted receptor cDNA fragment was confirmed. Reactions to determine nucleotide sequences were carried out using a DyeDeoxy Terminator Cycle Sequence Kit (Parkin Elmer Co.), and decoded using a fluorescent light automatic sequencer. The sequences of the 3 clones obtained were analyzed, and it was confirmed that all of them match the

reported gene sequence (SEQ ID NO: 4) in which the Sal I recognition sequence was added to the 5' side and the Spe I recognition sequence was added to the 3' side of the cDNA sequence (Lakaye, B., et al., Biochim. Biophys. Acta, Vol. 1401, pp. 216-220 (1998), accession No. AF08650) coding rat SLC-1 protein (SEQ ID NO: 3).

Reference Example 1-3

Preparation of CHO cells for rat SLC-1 expression

[0868] The full-length amino acid sequence of rat brain originated SLC-1, which was confirmed in Reference Example 1-2, was coded, and plasmid was prepared using a plasmid Midi Kit (Qiagen) from the E. coli transformed by the plasmid, to which the gene with Sal I recognition sequence added to the 5' side and Spe I recognition sequence added to the 3' side, had been introduced. Then, the insert section was cut out by digesting with Sal I and Spe I. The insert DNA was cut out with a razor from the agarose gel after electrophoresis.

[0869] Next, fragmentation, phenol extraction, phenol-chloroform extraction, and ethanol precipitation, were conducted and the DNA was recovered. This insert DNA was added to vector plasmid pAKKO-111H (the same vector plasmid as pAKKO1.11H described in Hinuma, S., et al., Biochim. Biophys. Acta, Vol. 1219, pp. 251-259 (1994)) for animal cell expression which was digested with Sal I and Spe I, and ligation was conducted using T4 ligase (TaKaRa Shuzo), to construct pAKKO-SLC-1 plasmid for protein expression.

[0870] After E. coli DH5 (TOYOBO) transformed by pAKKO-SLC-1 was cultured, pAKKO-SLC-1 plasmid DNA was prepared using a Plasmid Midi Kit (Qiagen). This was introduced into CHO dhfr$^-$ cells in accordance with the attached protocol, using a CellPhect Transfection Kit (Amersham Pharmacia Biotech Co.). A coprecipitating suspension of 10 μg of DNA and calcium phosphate was prepared, and this suspension was added to 10 cm Petri dishes in which 5×10^5 or 1×10^6 of CHO dhfr$^-$ cells had been seeded 24 hours previously. After these cells were cultured for 1 day in MEMα culture medium containing 10% fetal bovine serum, subculture was conducted, and cultivation was conducted in selective culture medium, MEMα culture medium containing no nucleic acid but containing 10% dialyzed fetal bovine serum. 56 Clones of colonies of the transformed CHO cells expressing SLC-1, proliferated in the selective culture medium, were selected.

Reference Example 1-4

Selection of CHO/SLC-1 cell strain expressing a large quantity of full-length rat SLC-1 receptor protein mRNA

[0871] The quantity of expressed full-length rat SLC-1 receptor protein mRNA of 56 clones of the CHO/SLC-1 strains established in Reference Example 1-3, was measured using a Cytostar T Plate (Amersham Pharmacia Biotech Co.) as shown below according to the attached protocol. Each well of the Cytostar T Plate was seeded with each clone of the CHO/SLC-1 strain by 2.5×10^4, and cultured for 24 hours, then the cells were fixed using 10% formalin. After 0.25% Triton X-100 was added to each well to increase cell permeability, ^{35}S-labeled riboprobes with SEQ ID NO: 5 were added and hybridized. 20 mg/ml of RNaseA was added to each well to digest free riboprobes. After the plate was thoroughly washed, the radioactivity of the hybridized riboprobes was determined using a Topcounter. Strains with high radioactivity showed large amounts of mRNA expression. In particular, mainly used was Clone number 44 among 3 clones which showed large amounts of mRNA expression.

Reference Example 1-5

Isolation of plasmid containing human SLC-1 cDNA

[0872] After nicks were inserted into the DNA of Human fetal brain originated cDNA library (SUPERSCRIPT™ cDNA Library; GIBCOBRL Co.) according to the manual of the Genetrapper cDNA positive selection system (GIBCOBRL Co.), using pharge F1 endonuclease, single stranded human fetal brain originated cDNA library was prepared by digesting the above-mentioned library with Escherichia coli exonuclease III.

[0873] Biotin-14-dCTP was added to the 3' end of synthetic oligonucleotide (equivalent to 1434-1451 of accession No. U71092), SEQ ID NO: 6 which was prepared according to the report by Kolakowski Jr., et al. (Kolakowski Jr., et al. (1996) FEBS Lett. Vol. 398, pp. 253-258) using Terminal Deoxynucleotidyl Transferase, and biotinated oligonucleotide was prepared. The above manual was followed regarding composition of a reaction mixture and reaction time.

[0874] After 4 μg of single stranded human fetal brain originated cDNA library was kept at 95°C for 1 minute, the library was rapidly cooled on ice. 20 ng of Biotinated oligonucleotide was added, which was hybridized using the attached hybridization buffer at 37°C for 1 hour. Streptoavidin beads were added to the mixture, then single stranded human fetal brain originated cDNA hybridized by biotinated oligonucleotide, was isolated using a MAGNA-SEP Mag-

netic Particle Separator (GIBCOBRL Co.). The complementary strand was synthesized according to the manual, using as primer 50 ng of synthetic oligonucleotide (equivalent to 1011 - 1028 of accession No. U71092) of SEQ ID NO: 7, prepared based on the report by Kolakowski Jr., et al (Kolakowski Jr., et al. (1996) FEBS Lett. Vol. 398, pp. 253-258), to give the double stranded plasmid.

Reference Example 1-6

Determination of nucleotide sequence of plasmid containing isolated human SLC-1 cDNA

[0875] After the plasmid obtained in Reference Example 1-5 was introduced into ELECTROMAX™DH10B™ Cells by the electroporation method, clones with cDNA inserted fragments were selected in LB agar culture medium containing ampicillin and X-gal. Using a sterilized toothpick, only the clones showing white color were separated to give transformant E. coli DH10B/hSLC-1. Individual clones were cultured overnight in LB culture medium containing ampicillin, and the plasmid DNA was refined using QIA prep8 mini prep (Qiagen). The reactions to determine nucleotide sequence were conducted using a DyeDeoxy Terminator Cycle Sequence Kit (Parkin Elmer Co.), and the nucleotide sequence was decoded using a fluorescent light automatic sequencer.

[0876] As the results, obtained was the sequence shown in SEQ ID NO: 8. The amino acid sequence (SEQ ID NO: 9) coded by the nucleotide sequence obtained here, differs from the human SLC-1 amino acid sequence predicted as the sequence analogized from rat SLC-1 based on human chromosome DNA sequence (accession number: Z86090) containing human SLC-1 sequence, in the report by Lakaye, et al. (Lakaye, B., et al. (1998) Biochim. Biophys. Acta. Vol. 1401, pp. 216-220). This shows the presence of ATG, the initiation codon, on mRNA, in the 69 and 64 amino acids upstream from the estimated sequence. Escherichia coli DH10B/phSLC1L8, the transformant produced by the plasmid containing DNA coding this sequence was deposited at IFO and NIBH.

Reference Example 1-7

Amplification of human SLC-1cDNA by PCR method using human fetal brain originated cDNA

[0877] Amplification by the PCR method was conducted using as the template plasmid containing human SLC-1 DNA sequence cloned by the gene trap method, and using synthetic DNA primers of SEQ ID NO: 10 and SEQ ID NO: 11, and synthetic DNA primers of SEQ ID NO: 12 and SEQ ID NO: 13, respectively. The former amplified DNA and the latter amplified DNA were named as "human SLC-1(S)" and "human SLC-1(L)", respectively. The synthetic DNA primer was constructed so that the genes in the domain translated to the receptor protein were amplified. At that time, a recognition sequence for each restriction enzyme was added to the 5' side and 3' side, so that the nucleotide sequence recognized by restriction enzyme Sal I would be added to the 5' side of the gene, and the nucleotide sequence recognized by restriction enzyme Spe I would be added to the 3' side. The composition of the reaction mixture for human SLC-1(S) amplification was: 5 μl of plasmid template containing human SLC-1 DNA sequence, 0.4 μM of respective synthetic DNA primers, 0.2 mM of dNTPs and 0.5 μl of Pfu DNA polymerase and buffers attached to the enzyme, with setting total quantity for reaction at 50 μl. A thermal cycler (Parkin Elmer Co.) was used for the cycles for amplification. After heating at 94°C for 60 seconds, the cycle consisting of 94°C for 60 seconds, 57°C for 60 seconds, and 72°C for 150 seconds, was repeated 25 times, and finally the temperature of the reactant was maintained at 72°C for 10 minutes. The composition of the reaction mixture for human SLC-1(L) amplification was 5 μl of plasmid template containing human SLC-1 DNA sequence, 0.4 μM of respective synthetic DNA primers, 0.2 mM of dNTPs, 0.5 μl of Pfu DNA polymerase and buffers attached to the enzymes, with setting total quantity for reaction at 50 μl. A thermal cycler (Parkin Elmer Co.) was used for the cycles for amplification. After heating at 94°C for 60 seconds, the cycle consisting of 94°C for 60 seconds, 60°C for 60 seconds, and 72°C for 3 minutes, was repeated 25 times, and finally the temperature of the reactant was maintained at 72°C for 10 minutes. After 0.8% agarose gel electrophoresis, confirmation of amplified products was conducted by ethidium bromide dying.

Reference Example 1-8

Subcloning of PCR product into plasmid vector and confirmation of amplified cDNA sequence by decoding of nucleotide sequence of inserted cDNA section

[0878] The reaction product after PCR in Reference Example 1-7 was separated using 0.8% low-melting point agarose gel, and the band section was cut out using a razor. After that, fragmentation, phenol extraction, phenol-chloroform extraction, and ethanol precipitation were conducted, and the DNA was recovered. The recovered DNA was subcloned into pCR-Script Amp SK(+) plasmid vector, as prescribed by the PCR-Script™ Amp SK(+) cloning kit (Stratagene Co.).

After this was introduced into Escherichia coli DH5α competent cells (TOYOBO) and transformed, the clones with cDNA inserted fragments were selected in LB agar culture medium containing ampicillin and X-gal. Using a sterilized toothpick, only clones showing white color were separated to give E. coli DH5α/hSLC-1(S), which is a transformant of human SLC-1 (S), and E. coli DH5α/hSLC-1(L), which is a transformant of human SLC-1 (L). Each clone was cultured overnight in LB culture medium containing ampicillin, and plasmid DNA was prepared using QIA prep8 mini prep (Qiagen). Some of the prepared DNA was digested with Sal I and Spe I restriction enzymes, and the size of the receptor cDNA fragments inserted was confirmed. The reactions to determine nucleotide sequence were conducted using a DyeDeoxy Terminator Cycle Sequence Kit (Parkin Elmer Co.) and the nucleotide sequence was decoded using a fluorescent light automatic sequencer. The sequence of the obtained clones respectively matched the DNA sequence (SEQ ID NO: 14) which should be amplified by synthetic DNA primers of SEQ ID NO: 10 and SEQ ID NO: 11 using human SLC-1 gene as a template, and the DNA sequence (SEQ ID NO: 15) which should be amplified by synthetic DNA primers of SEQ ID NO: 12 and SEQ ID NO: 13 using human SLC-1 gene as a template.

Reference Example 1-9

Preparation of CHO cells for expression of human SLC-1(S), and CHO cells for expression of human SLC-1(L)

[0879] Plasmid was prepared from the E. coli clones transformed by the plasmid wherein inserted were human SLC-1(S) and human SLC-1(L) whose sequences were confirmed in Reference Example 1-8, using a Plasmid Midi Kit (Qiagen), and the insert section was cut out using Sal I and Spe I restriction enzymes. After electrophoresis was conducted, the insert DNA was cut out from agarose gel using a razor. Next, fragmentation, phenol extraction, phenol-chloroform extraction, and ethanol precipitation were conducted, and the insert DNA was recovered.

[0880] This insert DNA was added to pAKKO-111H vector plasmid for animal cell expression, digested with Sal I and Spe I (the same vector plasmid as the pAKKO1.11H described in Hinuma, S., et al., Biochim. Biophys. Acta, Vol. 1219, pp. 251-259 (1994)), and ligation was conducted by adding T4 ligase (TaKaRa Shuzo), to construct pAKKO-hSLC-1(S) and pAKKO-hSLC-1(L) plasmids for protein expression.

[0881] After E. coli DH5α (TOYOBO) transformed by pAKKO-hSLC-1(S) and pAKKO-hSLC-1(L) was cultured, pAKKO-hSLC-1(S) and pAKKO-hSLC-1(L) plasmid DNAs were prepared using a Plasmid Midi Kit (Qiagen). These were introduced into CHO dhfr$^-$ cells in accordance with the attached protocol, using a CellPhect Transfection Kit (Amersham Pharmacia Biotech Co.). A coprecipitative suspension of 10 μg of DNA with calcium phosphate was made, which was added to 10 cm Petri dishes seeded 24 hours in advance with 5×10^5 or 1×10^6 CHO dhfr$^-$ cells. After the above was cultured for 1 day in MEMα culture medium containing 10% fetal bovine serum, subculture was conducted, and then cultivation was conducted in MEMα culture medium containing no nucleic acid but containing 10% dialyzed fetal bovine serum, which is a selective culture medium. 56 clones of colonies of transformed cells which are human SLC-1(S) gene introduced CHO cells, and 61 clones of colonies of transformed cells which are human SLC-1(L) gene introduced CHO cells, both of which proliferated in the selective culture medium, were selected.

Reference Example 1-10

Selection of cell colonies into which genes with large quantities of human SLC-1(S) and human SLC-1 (L) mRNA expression have been introduced

[0882] The quantities of expressed mRNA of 56 clones of CHO/hSLC-1(S) colonies and 61 clones of CHO/hSLC-1(L) colonies, both of which were established in Reference Example 1-9, were measured in accordance with the attached protocol using a Cytostar T Plate (Amersham Pharmacia Biotech Co.) as shown below.

[0883] After each well of the Cytostar T Plate was seeded with each clone of CHO/hSLC-1(S) colonies and CHO/hSLC-1(L) colonies by 2.5×10^4, and cultured for 24 hours, the cells were fixed using 10% formalin.

[0884] After 0.25% Triton X-100 was added to each well to increase cell permeability, ^{35}S-labeled riboprobe of SEQ ID NO: 16 was added and hybridization was conducted.

[0885] 20 mg/ml of RNaseA was added to each well to digest free riboprobe. After the plate was washed well, the radioactivity of the hybridized riboprobe was determined using a Topcounter. Colonies showing high radioactivity expressed large quantities of mRNA. Of the 7 clones which expressed large quantities of mRNA, mainly used was Clone number 57.

Experimental Example 1

Determination of antagonist activity using GTPγS binding assay of test compound

[0886] Membrane fraction was prepared by the following method, using the human SLC-1 expressing CHO cell clone 57 obtained in Reference Example 1-10, and the rat SLC-1 expressing CHO cell clone 44 obtained in Reference Example 1-4.

[0887] The human and rat SLC-1 expressing CHO cells (1×10^8) were scraped in buffer saline phosphate (pH 7.4) to which 5 mM EDTA (ethylenediaminetetraacetic acid) had been added, and centrifuged. 10 ml of homogenized buffer (10 mM $NaHCO_3$, 5 mM EDTA, pH 7.5) was added to the cell pellets, and they were homogenized using a Polytron homogenizer. The supernatant obtained by centrifugation at 400 × g for 15 minutes was further centrifuged at 100,000 × g for 1 hour, to obtain the membrane fraction precipitate. This precipitate was suspended in 2 ml of assay buffer [50 mM Tris-HCl(pH 7.5), 1 mM EDTA, 0.1% BSA (bovine serum albumin), 10 mM $MgCl_2$, 100 mM NaCl, 1 μM GDP (guanosine 5'-diphosphate), 0.25 mM PMSF (phenylmethylsulfonyl fluoride), 1 mg/ml pepstatin, 20 mg/ml leupeptin, 10 mg/ml phosphoramidon], which was centrifuged at 100,000 × g for 1 hour. The membrane fraction recovered as precipitate was suspended again in 20 ml of assay buffer, and after the suspension was divided, individual portions were preserved at -80°C and thawed before every use.

[0888] Determination of antagonist activity of the test compound was conducted as shown below. After 171 μl of SLC-1 expressing CHO cell membrane fractions diluted with assay buffer was poured into each well of a 96-well polypropylene plate, 2 μl of 3×10^{-10}M MCH diluted with DMSO solution, 2 μl of test compound solution diluted to various concentrations, and 25 μl of [^{35}S]-Guanosine 5'-(γ-thio) triphosphate (produced by Daiichi Kagaku Yakuhin) were added respectively. (Final concentration of cell membrane: 20 μg/ml, final concentration of [^{35}S]-Guanosine 5'-(γ-thio) triphosphate: 0.33 nM).

[0889] After this reaction mixture was allowed to react at 25 °C for 1 hour under stirring, it was filtered under vacuum using a glass filter (GF-C), then the filter was washed 3 times with 300 μl of washing solution (50 mM Tris-HCl buffer solution pH 7.5). 50 ml of liquid scintillator was added to the glass filter, and residual radioactivity was determined using a liquid scintillation counter.

[0890] The IC_{50} value of the compound was calculated from the binding inhibition rate (%), based on the definition that the binding inhibition rate (%) = (radioactivity when compound and MCH were added - radioactivity when DMSO solution was added)/(radioactivity when MCH was added - radioactivity when DMSO solution was added) × 100.

[0891] The results were shown below.

Compound Number	Inhibition Activity (IC_{50} value: μM)
Example 1	0.3
Example 5	0.02

Industrial Applicability

[0892] Compounds (I), (I'), (I''), (I''') and salts thereof possess excellent MCH receptor antagonistic activities, and are useful as an agent for preventing or treating obesity, etc.

SEQUENCE LISTING

<110> Takeda Chemical Industries, Ltd.

<120> Melanin Concentrating Hormone Antagonist

<130> 2728WOOP

<150> JP 2001-116219

<151> 2001-04-13

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Val Val Lys Lys Ser Lys Leu His Trp Cys Ser Asn Val Pro Asp Ile
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Phe Ile Ile Asn Leu Ser Val Val Asp Leu Leu Phe Leu Leu Gly Met
85 90 95

Pro Phe Met Ile His Gln Leu Met Gly Asn Gly Val Trp His Phe Gly
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Glu Thr Met Cys Thr Leu Ile Thr Ala Met Asp Ala Asn Ser Gln Phe
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Thr Val His Pro Ile Ser Ser Thr Lys Phe Arg Lys Pro Ser Met Ala
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Gly Cys Gly Ile Arg Leu Pro Asn Pro Asp Thr Asp Leu Tyr Trp Phe
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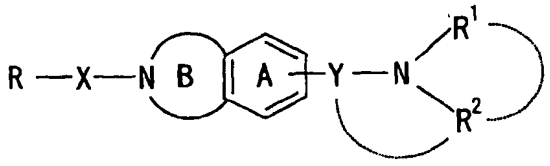
Claims

1. A melanin-concentrating hormone antagonist which comprises a compound represented by the formula:



(I)

wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
Y is a spacer having a main chain of 1 to 6 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted; and
R^1 and R^2 are the same or different and are hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic ring which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing heterocyclic ring which may be substituted;
or a salt thereof.

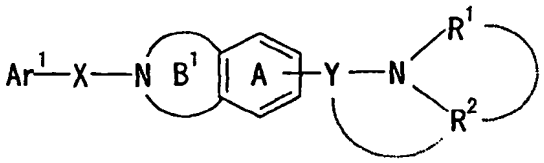
2. The antagonist according to claim 1, wherein R is a cyclic group which may be substituted; X is a spacer having a main chain of 1 to 6 atoms; and R^1 and R^2 are the same or different and are hydrogen atom or a hydrocarbon

group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, form a nitrogen-containing heterocyclic ring which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, form a nitrogen-containing heterocyclic ring which may be substituted.

3. The antagonist according to claim 1 which is an agent for preventing or treating diseases caused by melanin-concentrating hormone.

4. The antagonist according to claim 1 which is an agent for preventing or treating obesity.

5. A compound represented by the formula:



(I')

wherein Ar^1 is a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
Y is a spacer having a main chain of 1 to 6 atoms;
ring A is benzene ring which may be further substituted;
ring B^1 is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted; and
R^1 and R^2 are the same or different and are hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic ring which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing heterocyclic ring (except piperidine) which may be substituted;
provided that, when X is CO, ring B^1 is not azepane or 4,5-dihydroazepine each of which may be further substituted, or Ar^1 is not biphenylyl which may be substituted, and that Y is not $-CO-(C(Ra)H)_{na}-$ (Ra is hydrogen atom or a hydrocarbon group which may be substituted, na is an integer of 1 to 10) and does not have a bicyclic nitrogen-containing heterocyclic ring substituted with amino group; or a salt thereof.

6. The compound according to claim 5, wherein X is a spacer having a main chain of 1 to 6 atoms; and R^1 and R^2 are the same or different and are hydrogen atom or a hydrocarbon group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, form a nitrogen-containing heterocyclic ring which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, form a nitrogen-containing heterocyclic ring (except piperidine) which may be substituted.

7. The compound according to claim 5, wherein the cyclic group represented by Ar^1 is an aromatic group.

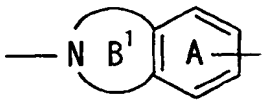
8. The compound according to claim 7, wherein the aromatic group is a group formed by removing an optional one hydrogen atom from an aromatic ring assembly formed by 2 or 3 members selected from C_{6-14} monocyclic or condensed polycyclic aromatic hydrocarbon and 5- to 10-membered aromatic heterocyclic ring.

9. The compound according to claim 5, wherein the spacer represented by X and Y is a bivalent group consisting of 1 to 3 members selected from -O-, -S-, -CO-, -SO-, $-SO_2-$, $-NR^8-$ (R^8 is hydrogen atom, optionally halogenated C_{1-6} alkyl, optionally halogenated C_{1-6} alkyl-carbonyl or optionally halogenated C_{1-6} alkylsulfonyl), and a divalent C_{1-6} non-cyclic hydrocarbon group which may be substituted.

10. The compound according to claim 5, wherein X is CO.

11. The compound according to claim 5, wherein Y is C_{2-6} alkenylene which may be substituted.

12. The compound according to claim 5, wherein the group represented by the formula:



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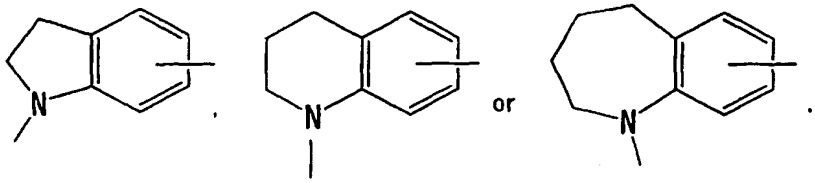


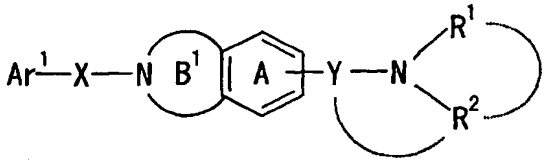
13. The compound according to claim 5, wherein R^1 and R^2, together with the adjacent nitrogen atom, form a nitrogen-containing heterocyclic ring which may be substituted.

14. The compound according to claim 5, wherein R^1 and R^5 are C_{1-6} alkyl.

15. A pharmaceutical composition comprising the compound according to claim 5, or a salt thereof.

16. A prodrug of the compound according to claim 5.

17. A process for producing a compound represented by the formula:

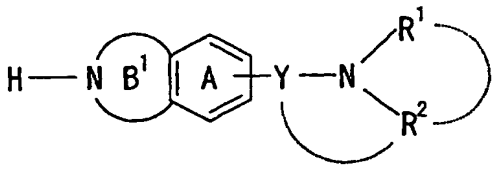


(I')

wherein each symbol is as defined in claim 5, or a salt thereof, which comprises reacting a compound represented by the formula:

$$Ar^1 - X - L \qquad \text{(IIb)}$$

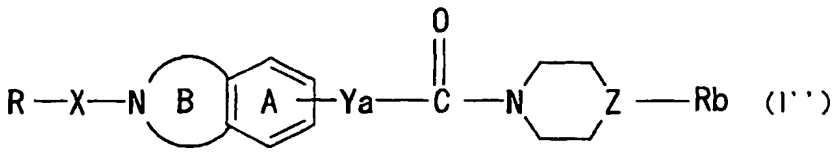
wherein L is a leaving group and the other symbols are as defined above, or a salt thereof with a compound represented by the formula:



(IIIb)

wherein each symbol is as defined above, or a salt thereof.

18. A compound represented by the formula:



wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
Ya is a spacer having a main chain of 1 to 5 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted;
Z is CH or N; and
Rb is hydrogen atom or a hydrocarbon group which may be substituted;
provided that Ya does not have a bicyclic nitrogen-containing heterocyclic ring substituted with amino group; or a salt thereof.

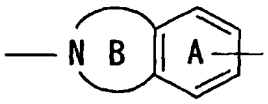
19. The compound according to claim 18, wherein R is hydrogen atom.

20. The compound according to claim 18, wherein Ya is $-(CH_2)_{w1}CO(CH_2)_{w2}-$ (w1 and w2 are an integer of 0 to 5 and w1 + w2 is 0 to 5).

21. The compound according to claim 18, wherein Z is CH.

22. The compound according to claim 18, wherein Rb is C_{6-14} aryl which may be substituted.

23. The compound according to claim 18, wherein the group represented by the formula:



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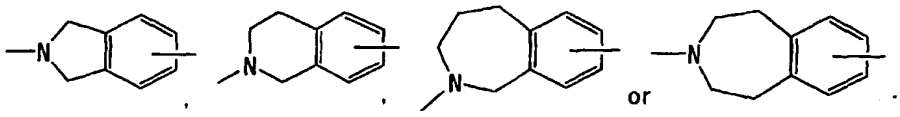
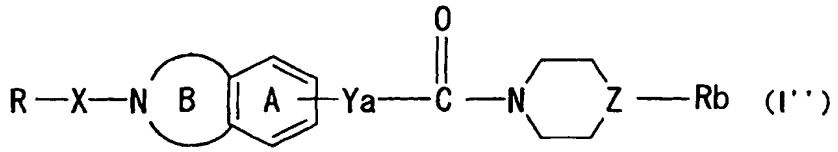


24. A pharmaceutical composition comprising the compound according to claim 18, or a salt thereof.

25. A prodrug of the compound according to claim 18.

26. A process for producing a compound represented by the formula:

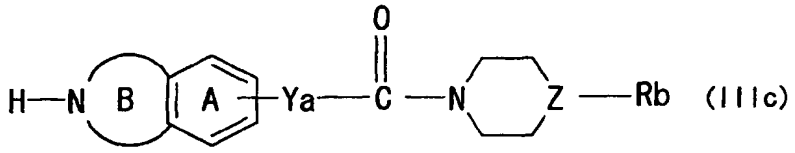


wherein each symbol is as defined in claim 18, or a salt thereof, which comprises reacting a compound represented

by the formula:

$$R—X—L \quad (IIa)$$

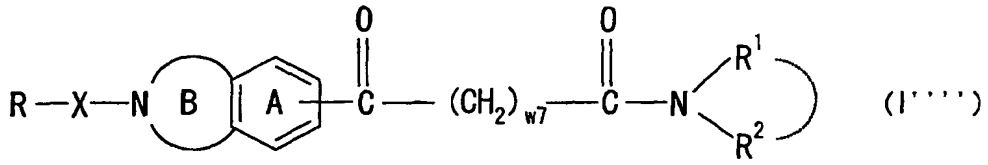
wherein L is a leaving group and the other symbols are as defined above, or a salt thereof, with a compound represented by the formula:



(IIIc)

wherein each symbol is as defined above, or a salt thereof.

27. A compound represented by the formula



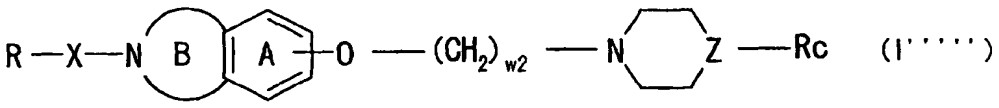
(I''''')

wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted;
w7 is an integer of 0 to 4; and
R^1 and R^2 are the same or different and are hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic ring which may be substituted; or a salt thereof.

28. A pharmaceutical composition comprising the compound according to claim 27 or a salt thereof.

29. A prodrug of the compound according to claim 27.

30. A compound represented by the formula:



(I''''''')

wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic group which may be further substituted;
w2 is an integer of 0 to 5;
Z is CH or N;
Rc is a hydrocarbon group which may be substituted; or a salt thereof.

31. The compound according to claim 30, wherein Z is CH.

32. The compound according to claim 30, wherein Rc is C_{6-14} aryl which may be substituted.

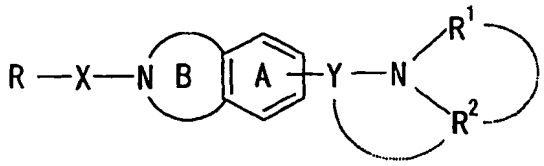
33. A pharmaceutical composition comprising the compound according to claim 30 or a salt thereof.

34. A prodrug of the compound according to claim 30.

35. The antagonist according to claim 1 which is an anorectic agent.

36. A pharmaceutical which comprises the melanin-concentrating hormone antagonist according to claim 1 in combination with at least one species selected from the group consisting of an agent for treating diabetes, an agent for treating hypertension and an agent for treating arteriosclerosis.

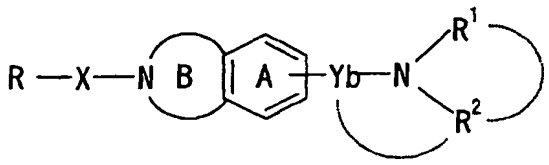
37. A method for preventing or treating diseases caused by a melanin-concentrating hormone in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound represented by the formula:



(I)

wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
Y is a spacer having a main chain of 1 to 6 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted; and
R^1 and R^2 are the same or different and are hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic rinc which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing heterocyclic ring which may be substituted;
or a salt thereof.

38. A method for preventing or treating obesity in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound represented by the formula:

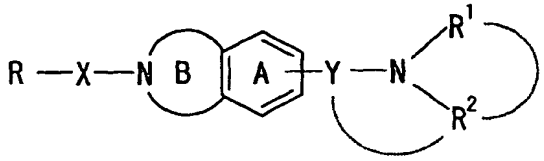


(I''')

wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
Yb is a spacer having a main chain of 1 to 6 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted; and
R^1 and R^2 are the same or different and are hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, may form a

nitrogen-containing heterocyclic ring (except piperidine) which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing heterocyclic ring which may be substituted;
provided that Yb is not $-CO-(C(Ra)H)_{na}-$ (Ra is hydrogen atom or a hydrocarbon group which may be substituted, na is an integer of 1 to 10);
or a salt thereof.

39. Use of a compound represented by the formula:

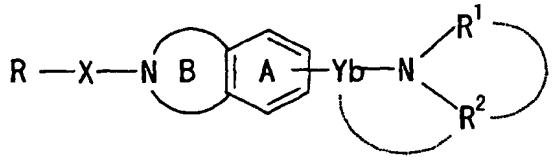


(I)

wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
Y is a spacer having a main chain of 1 to 6 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted; and
R^1 and R^2 are the same or different and are hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic ring which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing heterocyclic ring which may be substituted;
or a salt thereof, for the manufacture of a pharmaceutical preparation for preventing or treating diseases caused by a melanin-concentrating hormone.

40. Use of a compound represented by the formula:

a compound represented by the formula:



(I''')

wherein R is hydrogen atom, a halogen atom or a cyclic group which may be substituted;
X is a bond or a spacer having a main chain of 1 to 10 atoms;
Yb is a spacer having a main chain of 1 to 6 atoms;
ring A is benzene ring which may be further substituted;
ring B is a 5- to 9-membered nitrogen-containing non-aromatic heterocyclic ring which may be further substituted; and
R^1 and R^2 are the same or different and are hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted; or R^1 and R^2, together with the adjacent nitrogen atom, may form a nitrogen-containing heterocyclic ring (except piperidine) which may be substituted; or R^2, together with the adjacent nitrogen atom and Y, may form a nitrogen-containing heterocyclic ring which may be substituted;
provided that Yb is not $-CO-(C(Ra)H)_{na}-$ (Ra is hydrogen atom or a hydrocarbon group which may be substituted, na is an integer of 1 to 10);
or a salt thereof, for the manufacture of a pharmaceutical preparation for preventing or treating obesity.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07D209/08, 209/14, 215/12, 223/16, 265/36, 401/06, 401/12, 401/14, 403/06, 403/12, 405/12, 405/14, A61K31/404, 454, 4709, 4725, 538, 541, 55, 551, A61P3/04, 43/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07D209/08, 209/14, 215/12, 223/16, 265/36, 401/06, 401/12, 401/14, 403/06, 403/12, 405/12, 405/14, A61K31/404, 454, 4709, 4725, 538, 541, 55, 551, A61P3/04, 43/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS, REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/23437 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 27 April, 2000 (27.04.00), RN=265100-47-8 etc.	1-7,9,13, 15-17,35,36, 39,40
A	& AU 9961236 A & JP 2000-186088 A & JP 2000-186091 A	8,10-12,14, 18-34
X	WO 98/46590 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 22 October, 1998 (22.10.98), RN=153031-86-8 etc. & AU 9868528 A & EP 975624 A1 & JP 11-310532 A	1-7,9,11,13, 15-17,35,36, 39,40
X	WO 96/30014 A1 (MERCK AND CO., INC.), 03 October, 1996 (03.10.96), RN=183270-26-0 & US 5631280 A & CA 2216526 A & AU 9653218 A & EP 817629 A1 & JP 11-503418 A	5-7,9,12,15-17
EX	WO 01/44226 A1 (PROTHERICS MOLECULAR DESIGN LIMITED), 21 June, 2001 (21.06.01), RN=313491-07-5	5-7,9,12,15-17

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"E" earlier document but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July, 2001 (23.07.01)	31 July, 2001 (31.07.01)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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PX	WO 01/12600 A1 (COR THERAPEUTICS, INC.), 22 February, 2001 (22.02.01), RN=327045-70-5 etc. (Family: none)	5-12,15-17
PX	WO 01/07412 A1 (BAYER AG), 01 February, 2001 (01.02.01), RN=321199-97-7 etc. & DE 19934272 A	5-7,9,10,15-17
PX	WO 00/77027 A2 (PROTHERICS MOLECULAR DESIGN LIMITED), 21 December, 2000 (21.12.00), RN=313491-07-5 & WO 00/77027 A3 & WO 01/44226 A1	5-7,9,12,15-17
PX	WO 00/76970 A2 (ELI LILLY AND COMPANY), 21 December, 2000 (21.12.00), RN=313491-07-5 (Family: none)	5-7,9,12,15-17
PX	WO 00/76966 A2 (BAYER AG), 21 December, 2000 (21.12.00), RN=313689-24-6 etc. & DE 19927415 A	5-9,12,14-17
PX	JP 2000-321736 A (FUJI PHOTO FILM CO., LTD.), 24 November, 2000 (24.11.00), RN=307930-76-3 & US 6238856 A	5-7,9,12,17
PX	WO 00/64866 A1 (ASTRAZENECA AB), 02 November, 2000 (02.11.00), RN=303118-76-5 (Family: none)	5-7,9,12,15-17
PX	WO 00/42036 A1 (BASF AG), 20 July, 2000 (20.07.00), RN=284026-68-2 etc. (Family: none)	5-9,13-17
X	WO 00/15612 A1 (RHONE POULENC RORER LTD.), 23 March, 2000 (23.03.00), RN=261732-06-3 etc. & AU 9956343 A & EP 1114028 A1 & NO 2001000942 A	5-12,15-17
X	WO 99/62904 A1 (RHONE POULENC RORER PHARM. INC.), 09 December, 1999 (09.12.99), RN=209286-76-0 & AU 9943298 A & EP 1086099 A1 & NO 2000005912 A	5-7,9,13,15-17
X	WO 99/50237 A1 (HIDAKA HIROYOSHI), 07 October, 1999 (07.10.99), RN=245649-76-7 . & JP 11-279138 A & EP 1072587 A1	5-7,9,12,15-17
X	WO 99/43652 A1 (KISSEI PHARM.CO., LTD.) 02 September, 1999 (02.09.99), RN=239463-71-9 & AU 9925478 A & BR 9908301 A & EP 1057813 A1 & NO 2000004277 A	5-7,9,11,12, 16,17

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/33798 A1 (YAMANOUCHI PHARM.CO., LTD.), 08 July, 1999 (08.07.99), RN=229636-68-4 etc. & AU 9916876 A	5-7,9,12,15-17
X	WO 99/00371 A1 (BOEHRINGER INGELHEIM PHARM. K.-G.), 07 January, 1999 (07.01.99), RN=219643-08-0 etc. & DE 19727117 A & AU 9887279 A & EP 991624 A1	5-7,9,12-17
X	WO 98/50346 A2 (SMITHKLINE BEECHAM PLC), 12 November, 1998 (12.11.98), RN=215950-87-1 etc. & WO 98/50346 A3 & AU 9875267 A	5-9,11,12, 14-17
X	WO 98/29407 A2 (HOECHST MARION ROUSSEL INC.), 09 July, 1998 (09.07.98), RN=210173-21-0,210173-15-2 etc. & WO 98/29407 A3 & US 6004977 A & AU 9854349 A & EP 950056 A2 & CN 1242012 A & BR 9714189 A & NO 9903180 A	5-7,9,13-19, 22-26
X	WO 98/25611 A1 (RHONE POULENC RORER PHARM.INC.), 18 June, 1998 (18.06.98), RN=209286-76-0 & AU 9855182 A & EP 944386 A1 & CN 1244798 A & BR 9713921 A & JP 2001-506630 A & ZA 9711207 A & NO 9902853 A	5-7,9,15-17
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X	WO 97/06158 A1 (ASTRA PHARM.LTD.), 20 February, 1997 (20.02.97), RN=175870-96-9 & BR 9509297 A & CN 1162310 A	5-7,9,15-17
X	WO 96/38471 A1 (PFIZER INC.), 05 December, 1996 (05.12.96), RN=185057-46-9 etc. & CA 2220055 A & EP 828754 A1 & JP 10-510511 A & NO 9602162 A & AU 9654554 A & CN 1143647 A & US 5936089 A & FI 9704368 A	5-10,13,15-17

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 96/6079 A1 (SMITHKLINE BEECHAM PLC), 29 February, 1996 (29.02.96) RN=178313-52-5 etc. & EP 777650 A1 & JP 10-504315 A & US 5817833 A	5-12,14-17
X	JP 7-330726 A (KISSEI PHARM.), 19 December, 1995 (19.12.95), RN=175837-69-1 etc. (Family: none)	5-7,9,11,12, 16,17
X	JP 7-330725 A (KISSEI PHARM.), 19 December, 1995 (19.12.95), RN=175837-45-3 etc. (Family: none)	5-7,9,11,12, 15-17
X	WO 96/01817 A1 (ASTRA AKTIEBOLAG), 25 January, 1996 (25.01.96), RN=175870-96-9 & AU 9524139 A & EP 759027 A1 & JP 10-500138 A & ZA 9508088 A & US 5807886 A & FI 9604463 A & NO 9604698 A & US 6117898 A	5-7,9,15-17
X	EP 634401 A1 (AMERICAN CIANAMID CO.), 18 January, 1995 (18.01.95), RN=167158-96-5 & US 5387685 A & JP 7-179422 A & CA 2128139 A & FI 9403392 A & NO 9402673 A & AU 9467501 A & ZA 9405211 A & HU 218478 A & CN 1114650 A & US 5550149 A & US 5561141 A & US 5639887 A	5-7,9,14-17
X	EP 656350 A1 (SQUIBB BRISTOL MYERS CO.), 07 June, 1995 (07.06.95), RN=166263-08-7 & CA 2132771 A & US 5547966 A & AU 9474463 A & JP 7-188151 A	5-7,9,15-17
X	EP 600675 A1 (KISSEI PHARM.CO., LTD.), 08 June, 1994 (08.06.94), RN=160969-34-6 etc. & CA 2110454 A & JP 6-220015 A & US 5387603 A & JP 11-269117 A	5-7,9-12,15-17
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	JP 6-16558 A (CHUGAI PHARM.CO., LTD.), 25 January, 1994 (25.01.94), RN=142165-82-0 etc. (Family: none)	5-7,9,12,13, 15-17
X	WO 94/02459 A1 (PFIZER INC.), 03 February, 1994 (03.02.94), RN=155135-44-7 & JP 6-041068 A & EP 651743 A1 & BR 9306762 A & CN 1085894 A & ZA 9305304 A & HU 70182 A & NO 9500212 A & US 5541218 A	5-9,11,12, 15-17
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X	EP 528369 A2 (THOMAE DR.KARL GMBH), 24 February, 1993 (24.02.93), RN=149354-54-1 etc. & DE 4127404 A1 & CA 2076311 A & NO 9203235 A & AU 9221119 A & JP 6-025227 A & ZA 9206205 A & IL 102847 A & US 5455348 A	5,6,9,15-17
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 300725 A1 (SMITH KLINE AND FRENCH LAB. LTD.), 25 January, 1989 (25.01.89), RN=125398-10-9 etc. & DK 8804006 A & AU 8819137 A & JP 1-040461 A & ZA 8805241 A & US 4866076 A	5-7,9,15-17
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X	EP 25864 A1 (CASSELLA A.-G.), 01 April, 1981 (01.04.81), RN=77771-26-7 etc. & DE 2934609 A & DK 8003518 A & FI 8002562 A & NO 8002435 A & US 4335123 A & SU 965354 A & AU 8061793 A & JP 56-034668 A & ES 494535 A & ZA 8005311 A & CA 1154015 A & IL 60927 A	5-7,9,10,12, 15-17
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

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Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

Continuation of Box No. I-2 of continuation of first sheet (1)

The subject matter of each of claims 1-36, 39, and 40 relates to an extremely large number of compounds. As mentioned above, the subject matters of these claims are known in view of an extremely large number of documents. On the other hand, the compounds specified in the description, which have specific chemical structures, are limited to an extremely small proportion of the claimed compounds. Virtually, it is extremely difficult to enumerate all the prior art documents which deny novelty/inventive step because of the tremendous number thereof. In addition, the description does not contain a sufficient support for the subject matters as stated above. Consequently, the subject matters do not comply with given requirements in such a degree that a meaningful international search can be made.

Incidentally, in this international search report, a search was made through prior art documents with respect to the compounds specified in the description.

Continuation of Box No. II of continuation of first sheet (1)

The subject matter of claim 1 relates to a melanin-concentrating hormone antagonist, while the subject matters of claims 5, 18, 27, and 30 relate to compounds. These subject matters, which each is described using a Markush form, each is known as described in a large number of publications as stated above. Since they do not have a special technical feature, e.g., having an important chemical structural element common thereto, this application does not comply with the requirement of unity of invention.

Form PCT/ISA/210 (extra sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/04015

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 37,38
because they relate to subject matter not required to be searched by this Authority, namely:

The subject matter of claims 37 and 38 falls under the category of methods for treatment of the human body by therapy.

2. ☒ Claims Nos.: 1-36,39,40
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See extra sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ *The additional search fees were accompanied by the applicant's protest.*
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)